Vol. 8 No. 3 September, 1949

ANNALS OF THE RHEUMATIC DISEASES

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THE SUBCUTANEOUS NODULES OF RHEUMATOID ARTHRITIS WITH LIPOID DEPOSITION*

BY

M. HORWITZ

From the Department of Clinical Medicine, University of Cape Town

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Introduction

Weber and Freudenthal (1936-7), Weber (1943, 1944, 1947, 1948), and Fletcher (1946, 1947) have noted the rare occurrence of subcutaneous nodules in rheumatoid arthritis which consisted almost entirely of lipoid, and have designated such cases by various names to differentiate them from the "common" type of rheumatoid arthritis subcutaneous nodule.

During the clinical examination of seventy cases of chronic rheumatoid arthritis in Cape Town, twenty cases were found to have one subcutaneous nodule or several nodules (Horwitz, 1948, 1949). Eleven nodules were removed by biopsy (from eight cases), and their macroscopic and histological features were examined. One of these nodules was found to differ from the other ten in being composed almost entirely of lipoid and thus resembling the two cases described by Weber and Fletcher. The case is described fully below. When the descriptions were compared it seemed that there might be some common pathogenesis of the pathological changes observed in the nodule of this case and in the nodules described by Weber and Fletcher.

Experimental staining with scarlet red of frozen sections of an additional nine nodules (from seven cases of rheumatoid arthritis) showed that lesser degrees of lipoid deposition are in fact commonly present in most "ordinary" nodules in rheumatoid arthritis. It is, therefore, suggested that this lipoid deposition forms the basis of the later development of those nodules encountered with grosser degrees of lipoid deposition. If so, then there is no justification for using special nomenclature to designate the lipoid nodule in the present case, or in the similar cases recorded in the literature.

Review of Literature

Weber (1944) has suggested the term "necrobiotic nodules of the rheumatoid arthritis type" to designate the well-known characteristic subcutaneous nodules of rheumatoid arthritis which were described by Dawson (1933), Collins (1937), and Bennett and others (1940). Weber noted that subcutaneous nodules occasionally occurred which differed in histological structure from the common type of nodules only by the deposition of lipoid material, and Fletcher (1946, 1947) has used the term "necrobiotic nodules of the rheumatoid arthritis type with lipoid deposition" to indicate this special type of subcutaneous nodule.

Weber has written several papers on this subject. They are largely concerned with periodic reports of a case of chronic rheumatoid arthritis which was first demonstrated by Weber and Freudenthal at the Royal Society of Medicine in December 1936. Further reports on this same case were made by Weber in 1943, 1944, 1947, and 1948. The result has been the unique opportunity of following up

* Extracted from a thesis accepted for the degree of M.D., University of Cape Town, 1948.

a case of great interest over a period of twelve years.

The patient, aged 35 in 1936, had rheumatoid arthritis for six months. The arthritis was accompanied by multiple subcutaneous nodules over the elbows, the olecranon ridges, the dorsum of the hands, the buttocks, the greater trochanters, the coccyx, and both acromial regions. Numerous smaller nodules were present on the ears and face, especially over the borders of the lips and nostril. Some of the subcutaneous nodules were reddish in appearance ; others were yellowish-red. They were firm in consistency. None of the nodules were painful or tender with the exception of the nodules over the elbows.

A biopsy of one of the nodules was examined and described in detail. The main feature was the presence of large masses of cells forming round or oval areas which were scattered irregularly between the bundles of collagen tissue in all parts of the cutis. These cells were so numerous that their mass exceeded that of the collagen tissue, the bundles of which were pressed aside. The cells were conspicuous by their size, up to four times the size of an epithelial cell. Most of the cells were multinucleated. The cytoplasm was well stained, well defined, and abundant. It was homogeneous and did not have a " foamy " structure. When sections were stained for fat with Sudan III, these cells in some areas showed no fat nor lipoid at all ; in other areas the cytoplasm was stained a faint red. There was " no double refraction ".

Weber (1944, 1947) was uncertain what these cells should be called. He hesitated to call them " xanthoma cells " or " foam cells ", as this name usually denotes that the cells are loaded with lipoid droplets. In the sections the cells showed either no lipoid or lipoid present in a diffuse form. There was no actual proof of the presence of cholesterol. He tentatively suggested that they might be " prexanthoma cells " at an " intermediate stage in development " towards typical " foam cells ". His alternative explanation was that the cells were " at the height of their development ", but contained some " special lipoid " which was responsible for their peculiar appearance. Weber (1944) at first designated this case as " a Syndrome of Rheumatoid Arthritis combined with Multiple Xanthomatous Connective Tissue Infiltrations ". The serum cholesterol was 230 mg. per 100 c.cm. of blood and 350 mg. per 100 c.cm. on two separate occasions, and was 110 mg. per 100 c.cm. after the patient was treated with a " fat-poor diet ".

The patient was next seen in 1941. He still had symptoms due to his arthritis, but there were " only remnants of the nodules on the hands and about the elbows ". In 1943 the patient had " functionally almost recovered " except for some residual stiffness of the right hip. Nodules were still detectable over the knuckles and the elbows. The latest report was made by Weber in 1948. The patient was back at work, felt quite well, and his weight had risen from 7 to 10 stone. The nodules on the elbows had been spontaneously absorbed, but a number were still present on both hands.

Weber (1948) has stated that he now prefers to call the patient's illness by the term " lipoid rheumatism ".

Fletcher (1946, 1947) has described another case of rheumatoid arthritis with subcutaneous nodules in which there was marked lipoid deposition but which differed in certain respects from Weber's case.

The patient was a male, aged 42. Nodules first appeared four years after the onset of arthritis. They appeared in very many sites—over the occiput, the scapular spines, the pelvic bones, the elbows, the wrists, the fingers, the greater trochanters, the knees, and the feet. There appear to have been about forty nodules according to the description given. The nodules were " pale " in colour. There was marked deterioration in the general health.

Biopsy examinations were made of four nodules situated over the olecranon process, the forearm, and the fingers. Widespread necrosis was the most striking feature in all the nodules. One nodule had the histological picture which is usually encountered in the characteristic nodules of rheumatoid arthritis, that is, central necrosis surrounded by mononuclear cells arranged in a palisade manner. Around most of the necrotic areas in the other nodules was a broad cellular band composed of typical " foam cells ". The cells were large and pale, and contained numerous very distinct vacuoles. These " foam cells " gave a positive Schultze test for cholesterol and showed fine orange-red droplets in sections stained with Sudan. Stained granules could be seen in the cells and filling the spaces between connective-tissue bundles. Cholesterol was also demonstrated by the Schultze test in the greater part of the necrosis and in the immediate surrounding tissues, that is, it was intracellular and extracellular. Multinucleated giant cells of the " foreign-body type " were frequently present. In some nodules the central necrotic zones were surrounded both by the characteristic mononuclear cells in palisade manner and by " foam cells ". Surrounding the cellular zone of " foam cells " or of mononuclear cells were connective-tissue bands which contained numerous lymphocytes, plasma cells, and well-defined " foam cells ". The blood vessels in the neighbourhood of the nodules, and in the nodules, often showed inflammatory changes.

Fletcher stressed that the basic histological

reactions of focal necrosis, cellular proliferation, round cell infiltration, and vascular lesions were present in these nodules, and that they differed from the nodules described by Collins (1937) largely in the altered cytology. The essential difference was the presence of cells which showed vacuoles, which contained cholesterol by Schultze's test, and which stained decisively with Sudan III. Fletcher suggested the term " necrobiotic nodules of the rheumatoid arthritis type with lipoid deposition " to describe his case, and he has classified it separately (1947).

The serum cholesterol was recorded twice in Fletcher's case ; the results were 135 and 154 mg. per 100 c.cm. of blood.

Weber and Fletcher could find no records of previous descriptions of similar cases in the literature, with the possible exception of a case described by Layani (1939) and by Layani and others (1939). Layani referred to his case as " xanthomatous chronic deforming rheumatism ", and Graham and Stansfield (1946) have summarized his descriptions.

The patient was a female of 46 years with chronic polyarthritis of fifteen years' duration. There was gross disorganization of the joints. She developed xanthoma *planum et tuberosum*, angina pectoris, prolonged jaundice with hepatomegaly, and marked hypercholesterolaemia. There was no autopsy report, and it is uncertain what the nature of the disease was. Probably it was a coincidental combination of rheumatoid arthritis with generalized primary xanthomatosis and xanthomatous biliary cirrhosis (Thannhauser, 1940).

Graham and Stansfield (1946) have described a case which presented with clinical features of polyarthritis resembling rheumatoid arthritis.

Cutaneous nodules appeared and increased progressively in size and number, and ill-defined nodules also developed in the subcutaneous tissue and in the muscles. Radiological examinations revealed patchy bone destruction of many parts of the skeleton. The histological examination of the nodules revealed widespread involvement by histiocytes with " foamy " cytoplasm. The microchemical tests for fat, lipoid, and glycogen in these cells were negative. After two to three years a nodule in the right axilla increased rapidly in size and assumed the appearance of a malignant tumour. The patient died, and the histological appearances of this tumour were those of a " polymorphic-celled sarcoma ". There was extremely widespread infiltration of certain mesodermal tissues by similar cells to those encountered in the original biopsy.

The authors suggested that this case should properly be classed among the lipoidoses, and they referred to it as " a case of a hitherto unrecognized lipoidosis simulating rheumatoid arthritis ". Bywaters (1949) agrees that their case was an example of a granulomatous infiltration of bones, joints, and tendons mimicking rheumatoid arthritis.

Raven and others (1948) described a case of rheumatoid arthritis with numerous subcutaneous and visceral nodules at autopsy. Frozen sections, stained for fat, showed intracellular sudanophil droplets in the cells surrounding the necrotic foci and extracellular granules throughout the central necrotic area. With the polarized light some of the intracellular lipoid appeared doubly refractive.

Kersley and others (1946) described various types of lipoid deposition in three nodules in a series of cases of rheumatoid arthritis. The main features of these nodules were as follows :

1. The nodule from their twelfth case had a typical histological appearance in part of the tissue characteristic of the " usual " necrobiotic nodule. Elsewhere in the nodule the structure was quite different. The central necrotic zone was heavily infiltrated by cholesterol, and the material yielded abundant cholesterol crystals when it was scraped. Foreign-body giant cells were seen in the tissues adjacent to the areas of lipoid infiltration, and appeared in some cases to be attempting to engulf adjacent cholesterol. No " foam cells " were seen. The surrounding fibrous tissue was more hyaline and less cellular than elsewhere.

2. The nodule from their thirteenth case showed a characteristic necrotic focus in one small area. The rest of the nodule consisted of two foci of cholesterol surrounded by numerous layers of dense hyaline eosinophilic fibrous tissue. Perivascular and paravascular-cell infiltrations were noted in the fibrous tissue and in the subcutaneous tissue.

3. The nodule from their fourteenth case was a " sausage-shaped " mass, which consisted of a fibrous capsule enclosing a " soft yellow greasy necrotic material ". Sections showed, in addition to granular amorphous debris, areas of " foam cells ". These " foam cells " were large, rounded, or polygonal cells with small darkly stained nuclei and well-defined cell membranes. The cytoplasm was vacuolated. Cholesterol clefts were present in hyaline fibrous tissue.

Case Report

The patient was an elderly European male aged 78 years, who had suffered from chronic rheumatoid arthritis for forty-three years. The proximal interphalangeal joints, metacarpophalangeal joints, wrists, elbows, shoulders, and knees were affected. These joints were constantly painful and stiff. He had never experienced a remission since the onset of the disease, but the degree of pain and swelling fluctuated. He considered that he was " at his worst " twelve years earlier. He lost 15 lb. in weight at the onset of the disease, but there was no further decrease in weight. Nodules developed painlessly on both elbows approximately twelve years ago. They attained the size of " walnuts ", but have since decreased considerably in size.

He was found to be in a fair state of general health. All the affected joints were slightly swollen and slightly tender, with limitation of movement. There was some ulnar deviation of the fingers, with wasting of the thenar and hypothenar eminences. There were no gross deformities or contractures. While he was under observation during 1947-8 he had an attack of coryza with acute pharyngitis, followed by an exacerbation of the features of the polyarthritis. The affected joints became very painful and more swollen. Several months later he had largely " recovered " from the relapse.

Subcutaneous nodules were present over both elbows. Two nodules were present on the left side, the proximal one being situated over the proximal end of the radius, and the distal one along the posterior border of the ulna, 2 inches distal to the tip of the olecranon process (Fig. 1). The nodules were each half an inch in diameter. The nodule over the head of the radius was soft in consistency, and the nodule over the ulnar border was firm and adherent to the underlying periosteum.

A soft mass was visible and palpable over the right olecranon process in the situation of the olecranon bursa. It consisted of soft tissue and did not fluctuate. In it could be palpated one discrete, firm, pea-sized nodule, and five tiny nodules, each the size of a pin's head, which were loosely adherent to each other.

No other abnormalities were noted with the exception of arteriosclerosis and slight hypertension. The urine and the blood count were normal.

The diagnosis was confirmed radiologically by the demonstration of characteristic changes in the hands and wrists. Some secondary osteo-arthritic changes were also detected.

The results of special investigations were as follows : sedimentation rate 40 mm. in 1 hour (Westergren) ; serum uric acid 3·5 mg. per 100 c.cm. ; serum cholesterol 139 mg. per 100 c.cm. ; blood urea 35 mg. per 100 c.cm. ; serum albumin 4·6 g. per 100 c.cm. ; serum globulin 2·7 g. per 100 c.cm. ; thymol turbidity 7 ; colloidal gold 5 ; thymol flocculation 4 ; Congo Red test, 61 per cent. of dye remained in the serum after one hour ; fractional test meal normal ; Wassermann reaction negative ; Brucella agglutination negative.

Biopsy of Subcutaneous Nodule.—The mobile nodule over the proximal end of the radius on the left side was removed (Fig. 2, upper specimen). Its surface was rounded and smooth and it felt fluctuant. A cross-section showed that it had a cyst-like structure. Its centre contained a large amount of yellow, greasy material which was partially detached from the wall of the nodule (Fig. 2, lower specimen). The yellow, greasy material consisted of characteristic cholesterol crystals (Fig. 3A), of debris, and of sudanophil lipoid droplets (Fig. 3B). A frozen section stained with Scarlet red showed the presence of large amounts of sudanophil lipoid in the tissues adjacent to the central area of cholesterol and lipoid (Fig. 4).

Fig. 5A illustrates a cross-section of the nodule under very low power. One of the poles and two of the side-walls of the nodule can be seen surrounding an empty space. It is this empty space which was filled with debris and the cholesterol crystals seen in Figs. 2 (lower specimen), 3A, and 3B. Two other similar but very much smaller spaces can be seen near the pole of the nodule situated in necrotic foci (Fig. 5A).

Fig. 5B illustrates a cross-section under a higher magnification. It can be clearly seen that the wall of the nodule is composed of two parts : (*a*) an outer layer of concentric connective tissue fibres, and (*b*) an inner layer which is undergoing necrosis and degenerating, and which merges with the debris in the centre of the nodule.

A few large foreign-body giant cells were seen at the junction of the inner and outer layers. No " foam cells " were seen.

Some small blood-vessels in the connective tissue at the periphery showed perivascular infiltration with lymphocytes. The sections were not examined with polarized light.

Discussion

This case is certainly an example of " lipoid deposition " in a nodule of rheumatoid arthritis. The lipoid deposition was so extensive that it comprised the major part of the nodule. Only a shell of fibrous connective tissue surrounded the large amount of cholesterol and sudanophil lipoid. From a survey of Figs. 2 to 5 the evolution of the changes which occurred may be surmised. The nodule had been present for a long time (twelve years) in a case of chronic rheumatoid arthritis. The original areas of necrosis which are present characteristically in these subcutaneous nodules (as in Fig. 6A) probably underwent liquefaction and lipoid material was deposited. The lipoid deposition proceeded to such an extent that the lipoid areas coalesced and came to occupy the entire centre of the nodule with a rim of fibrous tissue round it. The two small spaces seen in Fig. 5A are probably the sites of similar lipoid deposition in small necrotic foci at an earlier stage.

The problem arises as to the relationship of this case to those cases described by Weber and Freudenthal (1936-7) and Weber (1944, 1947, 1948) ; by Fletcher (1946, 1947) ; and by Kersley and others (1946). The macroscopical appearances of this nodule are not quite like those either of Weber's case or of Fletcher's case as no " foam cells " were seen and as all the lipoid appeared to be extracellular.

The nodule appears to be similar in some respects to the nodules described by Kersley and others (1946). The cholesterol deposition in their twelfth case differs only in degree from this case—the cholesterol deposition in their case was still restricted to certain areas of the nodule, whereas the deposition of cholesterol and of sudanophil lipoid in this case was so extensive that it practically replaced the entire nodule. Both nodules have the same

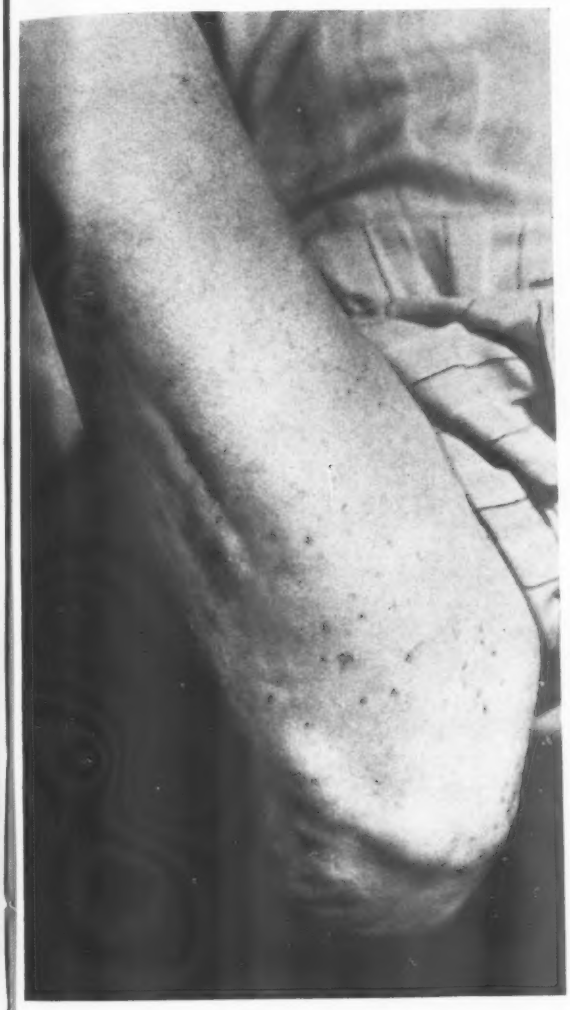
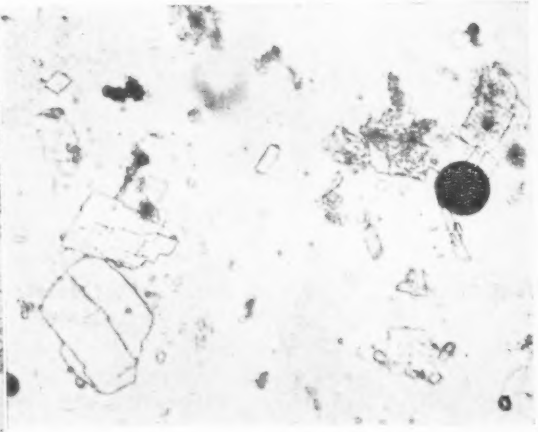


FIG. 1.—A man, aged 78 years, who had had rheumatoid arthritis for 43 years. Two subcutaneous nodules had been present on the left elbow for twelve years.

FIG. 2.—Biopsy of proximal subcutaneous nodule seen in Fig. 1. The nodule was cystic and on section was found to contain a large amount of yellow, greasy material.



FIGS. 3A (left : unstained) and B (right : Scarlet red).—The yellow greasy material in the centre of the nodule consisted of debris, of numerous characteristic cholesterol crystals (Fig. 3A), and of sudanophil lipoid droplets (Fig. 3B). (Note that in Fig. 3B cholesterol crystals are not stained by Scarlet red.)

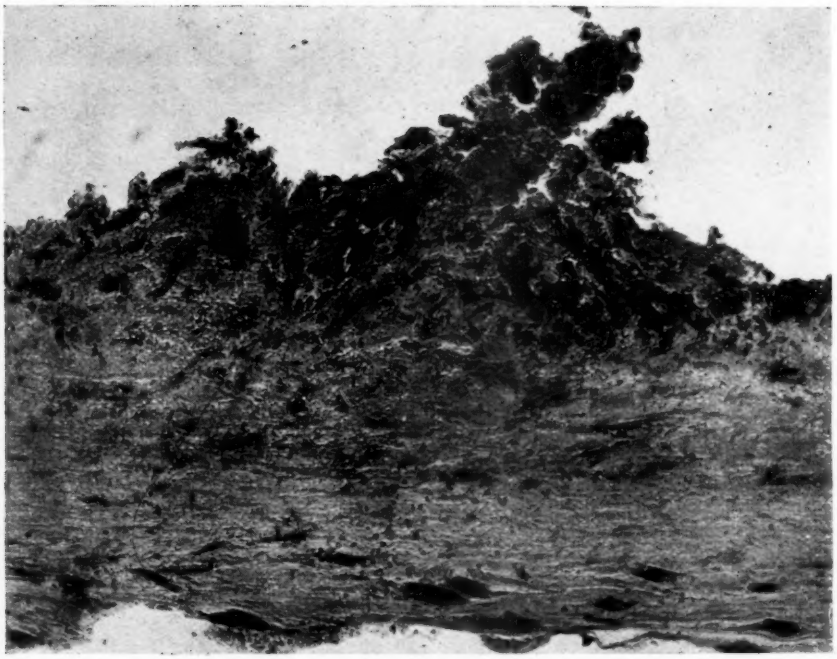


FIG. 4.—Large amounts of sudanophil lipoid are present in tissues surrounding the central mass of cholesterol and lipoid. (Frozen section: Scarlet red, ×95.)

surrounding hyaline fibrous tissue, and a few foreign-body giant cells were noted in both. Similarly, the nodule from their thirteenth case had a small central area of cholesterol and a thick surrounding wall of fibrous tissue, whereas the nodule of this case had a very large area of cholesterol and a thinner fibrous tissue wall. The macroscopic appearance of the nodule from their fourteenth case (the " sausage-shaped mass ") was strikingly similar to the features noted in this case, but numerous " foam cells " were present in addition on histological examination in their case. These " foam cells " were similar to the cells noted by Fletcher in his case.

On reviewing the cases described by Weber, by Fletcher, and by Kersley and others, it seems that a variety of lipoid changes may occur in these subcutaneous nodules of rheumatoid arthritis, and the present case is important as it helps to illustrate the sequence of events which may be occurring.

The problem becomes simplified if one postulates that the primary change is the deposition of a small amount of cholesterol or other lipoid in the central necrotic area of a focus in the nodule. Dawson (1933) had noted that cystic degeneration sometimes occurred in the necrotic areas of old nodules and was sometimes followed by the deposition of numerous cholesterol crystals, and Bywaters (1949) noted the common occurrence of cholesterol crystals in the central necrotic areas and of "foam cells "in the palisade layer. Raven and others (1948) quoted Professor Russell's opinion that sudanophil substances might be expected in the rheumatoid arthritis nodules with central necrosis. The subsequent appearance of the nodule probably depends merely on the amount of lipoid which is deposited; on the site of deposition, and on the reaction of the surrounding tissues to the presence of the lipoid. Kersley and others noted that foreign-body giant cells attempted to engulf lipoid in the nodule of their twelfth case.

Any or all of the following changes could conceivably then occur: presence of cholesterol crystals or of other lipoid material in small, moderate, or large amounts extracellularly; and presence of " foam cells " containing lipoids in variable amounts intracellularly. The resulting macroscopic and microscopic appearance of the nodule would depend on the extent to which these changes had occurred. Thus:

(*a*) In Weber's case the lipoid, of undetermined type, was situated wholly intracellularly, producing cells somewhat resembling " foam cells ".

(*b*) In Fletcher's case the lipoid was situated partly intracellularly, producing " foam cells ", and partly extracellularly in the connective tissue.

(*c*) In the thirteenth case (in the series of Kersley and others) the extracellular cholesterol deposition formed a *small* focus surrounded by dense fibrous tissue.

(*d*) In the twelfth case of Kersley and others' series the cholesterol was deposited extracellularly in *some* of the necrotic areas.

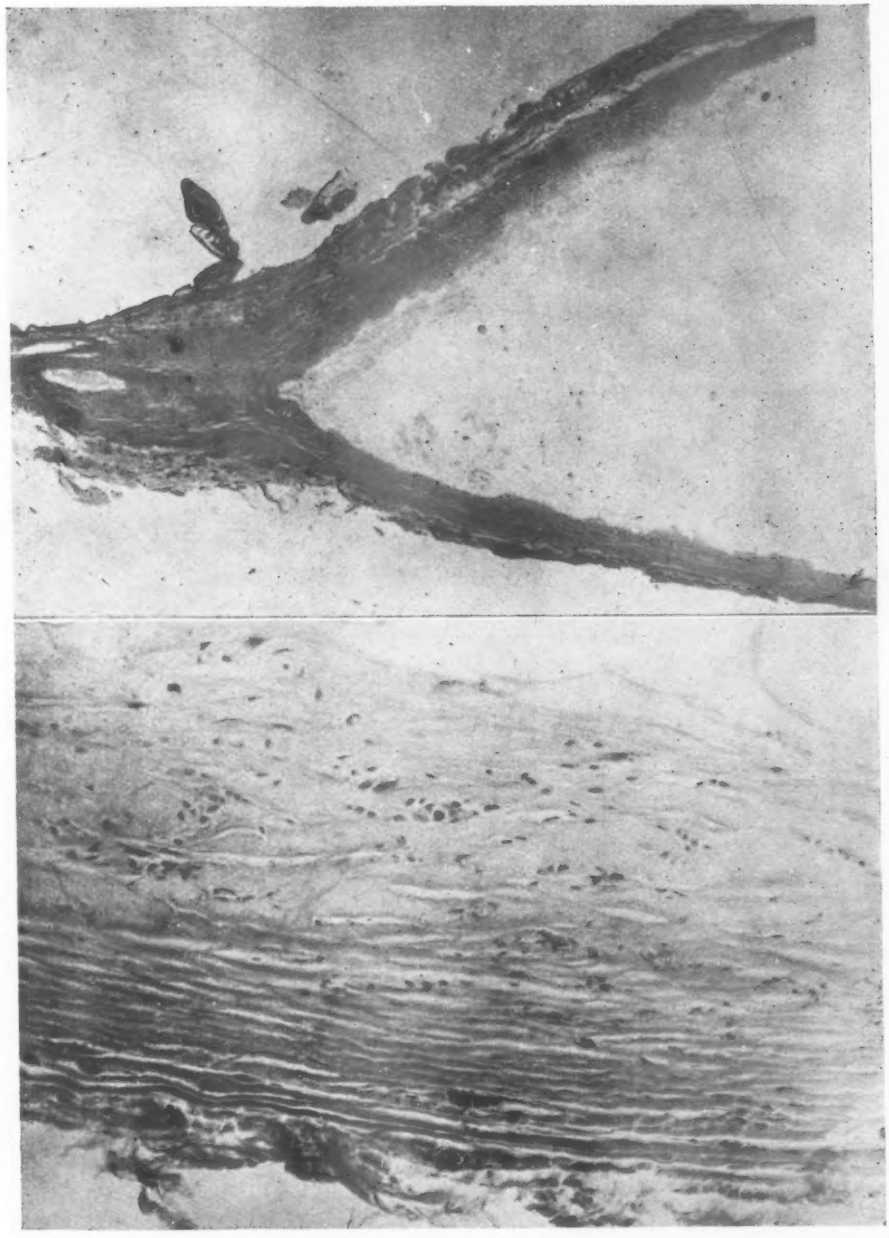


FIG. 5A.—The empty space between the edges of the nodule contained the mass of cholesterol crystals and lipoid seen in Figs. 3A and B. Two very similar but much smaller spaces are detected near the left pole of the nodule. (Haematoxylin and eosin, ×10.)

FIG. 5B.—Wall of nodule consisting of an outer concentric fibrous tissue layer and an inner layer which is partially necrotic. (Haematoxylin and eosin, ×130.)

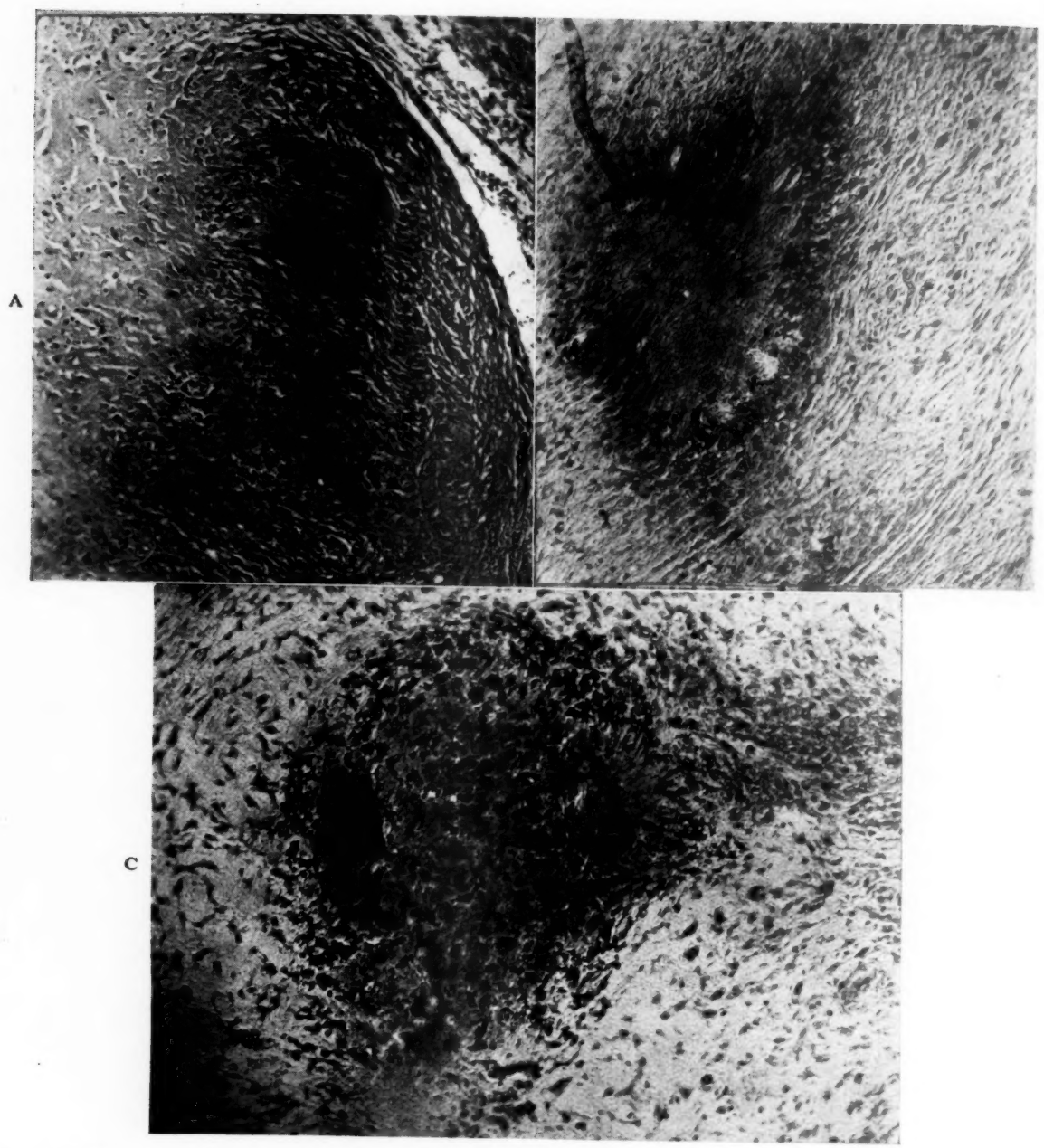


FIG. 6A.—Illustrates a typical focus commonly seen in the subcutaneous nodules of rheumatoid arthritis. It consists of a central zone of necrosis, surrounded by a palisade-like zone of radially-arranged mononuclear cells, and an outer zone of connective tissue. (Haematoxylin and eosin, ×95.)

FIG. 6B.—An example of a focus in which lipoid is demonstrable (with Scarlet red) at the periphery of a necrotic area. (Scarlet red, ×95.)

FIG. 6C.—An example of a focus in which lipoid is demonstrable throughout the necrotic area. (Scarlet red, × 95).

(Figs. 6A, B, and C are illustrations of sections from different nodules.)

(*e*) In the fourteenth case of Kersley and others' series there was lipoid deposition intracellularly, producing " foam cells " ; and also extracellularly, producing a large area of " soft, yellow greasy material " in the centre of the nodule.

(*f*) In the present case there was a *very extensive* extracellular deposition of cholesterol and sudanophil lipoid, which attained such a great size that it comprised more than three-quarters of the entire nodule. There was no intracellular deposition and no " foam cells " were noted.

If this theory is accepted it will link together all these cases with their variable degrees of lipoid deposition.

It is of interest to note that " lipoid deposition " may occur in gouty tophi. Chauffard and Troisier (1921) described the presence of cholesterol in tophi, and Kersley and others (1946) have noted the presence of " foam cells " containing cholesterol in a tophus of one of their cases with gout. They remarked on the resemblance of the " foam cells " of their case to the " foam cells " described by Fletcher (1946, 1947) in the nodule of his case mentioned above.

The occurrence of cholesterol deposition in gouty tophi, and the presence of " foam cells " in the case described by Kersley and others, lends further support to the hypothesis put forward to reconcile the diverse findings with regard to lipoid deposition in rheumatoid arthritis nodules. If both free cholesterol crystals and " foam cells " can occur in a gouty tophus, then it is understandable that either, or both together, might occur in rheumatoid arthritis nodules and produce a variety of histological appearances.

Conclusion.—The suggested conclusion is that the " special " nodules described by Weber and by Fletcher are possibly interesting variants of a fairly common pathological process, that is, the deposition of lipoid in the necrotic areas of the subcutaneous nodules. Bywaters (1949) has expressed the view that there seems to be no reason for separating such cases from the ordinary type of rheumatoid arthritis with nodules showing only a small amount of cholesterol.

Routine Examination of Rheumatoid Arthritis Subcutaneous Nodules for the Presence of Lipoid

After this case with marked lipoid deposition in the nodule was encountered it was decided to make routine examinations of other rheumatoid arthritis nodules for the presence of lipoid. Thus, frozen sections from an additional nine nodules (obtained by biopsy from seven cases) were stained with Scarlet red in the same manner and examined. They were compared with corresponding sections fixed in formalin and stained with haematoxylin and eosin.

The results were striking and interesting. Of the nine nodules examined in this manner there was sudanophil lipoid demonstrable in eight nodules, and no lipoid in one case. There was thus a high incidence of lipoid histologically in rheumatoid arthritis nodules as determined by this technique.

The distribution of the lipoid was confined to the areas of necrosis. Usually the lipoid was found in the peripheral part of the areas of necrosis (Fig. 6B), and occasionally the lipoid was present in both the peripheral and central parts of the necrotic areas (Fig. 6C). All these eight nodules in which lipoid could be detected had the characteristic histological appearances with multiple necrotic foci (as in Fig. 6A) when examined after staining with haematoxylin and eosin ; whereas the one nodule which contained no lipoid consisted almost entirely of connective tissue with only a minute area of necrosis when examined in the same way. The occurrence and the distribution of the lipoid are therefore closely related to the presence and distribution of the necrotic foci in the nodules. (The histological appearance of a characteristic focus with its central necrotic area surrounded by a " palisade " of mononuclear cells is seen in Fig. 6A.)

The presence of the lipoid was noted in nodules which originated outside the olecranon bursa as well as in nodules which originated in, or were attached to, the olecranon bursa.

With a knowledge of the high incidence of lipoid present microscopically in the nodules, it appears very probable that the lipoid can increase in extent as the necrotic areas merge and coalesce with each other. Ultimately the lipoid could occupy a large part of the nodule. " Foam cells " might appear if the lipoid was intracellular. Thus the lipoid deposition which occurs frequently in the necrotic areas is probably the starting point in the evolution of the nodules described by Weber (1944, 1947, 1948) ; by Fletcher (1946, 1947) ; by Kersley and others (1946) ; and in the evolution of the nodule described above in the present case.

The results of the investigation therefore tend to support the suggestions offered of the pathogenesis of the nodule in the present case and of similar nodules described in the literature.

The *serum cholesterol* was within normal limits in the present cases and in Fletcher's case, and it was slightly raised on one occasion in Weber's case.

These findings are not surprising as the local deposition of cholesterol in various conditions (for example, in inspissated pleural effusions, in hydrococele fluid, or in hydatid cysts) is neither due to, nor dependent on, hypercholesterolaemia.

Summary

1. A subcutaneous nodule removed from a case of rheumatoid arthritis was found to consist of a rim of fibrous tissue enclosing a large central

collection of cholesterol crystals and extracellular sudanophil lipoid.

2. The literature of other examples of rheumatoid arthritis nodules with lipoid deposition was reviewed, and the findings were compared with those in the above case.

3. Frozen sections were made from an additional nine subcutaneous nodules, and in eight instances the presence of lipoid could be demonstrated histologically in the characteristic necrotic foci in the nodules.

4. It is therefore suggested that the subcutaneous nodules of rheumatoid arthritis with lipoid deposition which have been described are not distinct entities, but are merely different histological end-results of a process with a common pathogenesis, that is, the deposition of lipoid in the necrotic foci in the nodules.

There seems, then, to be no special reason for separating such cases by special nomenclature from the ordinary type of rheumatoid arthritis with nodules containing little or no lipoid.

I wish to thank Prof. F. Forman for facilities in investigating cases under his care. I am also greatly indebted to Dr. G. Selzer for valuable assistance in the histological examinations ; to Prof. B. J. Ryrie and Prof. M. van den Ende for laboratory facilities ; to Mr. W. Taylor for the preparation of the histological material ; and to Mr. G. C. McManus for the photography.

References

Bennet, G. A., Zeller, J. W., and Bauer, W. (1940). *Arch. Path.*, **30**, 70.
Bywaters, E. G. L. (1949). *Annals of the Rheumatic Diseases*, **8**, 1.
Chauffard, A., and Troisier, J. (1921). *Ann. Med.*, **9**, 149. (Quoted by Kersley and others, 1946.)
Collins, D. H. (1937). *J. Path. Bact.*, **45**, 97.
Dawson, M. H. (1933). *J. exp. Med.*, **57**, 845.
Fletcher, E. (1946). *Annals of the Rheumatic Diseases*, **5**, 88.
—— (1947). "Medical Disorders of the Locomotor System." E. and S. Livingstone. Edinburgh.
Graham, G., and Stansfield, A. G. (1946). *J. Path. Bact.*, **58**, 545.
Horwitz, M. (1948). "Subcutaneous Nodules and Visceral Lesions of Chronic Rheumatoid Arthritis." M.D. Thesis, Cape Town.
—— (1949). *Clin. Proc.*, Vol. 8 (in the press).
Kersley, G. D., Gibson, H. J., and Desmarais, M. H. L. (1946). *Annals of the Rheumatic Diseases*, 5, 141.
Layani, F. (1939). *Bull. Soc. Med. Hop. Paris.* Third series. **55**, 343. (Quoted by Raven and others, *Annals of the Rheumatic Diseases*, 1948, **7**, 63.)
——, Laudat, M., and Astruc, P. (1939). *Ibid.*, 55, 355.
Raven, R. W., Weber, F. P., and Price, L. W. (1948). *Annals of the Rheumatic Diseases*, **7**, 63.
Thannhauser, S. J. (1940). "Lipidoses : Diseases of the Cellular Lipid Metabolism." New York, London, and Toronto. Oxford University Press.
Weber, F. P., and Freudenthal, W. (1936-7). *Proc. R. Soc. Med.*, **30**, 522.
—— (1943). *Brit. J. Derm.*, **55**, 1.
—— (1944). *Annals of the Rheumatic Diseases*, **4**, 3.
—— (1947). "Rare Diseases and Some Debatable Subjects." Second edition. Staples Press, Ltd., London.
—— (1948). *Brit. J. Derm. Syph.*, **60**, 106.

Nodules Sous-cutanés avec Dépots Lipoïdiques dans l'Arthrite Rhumatismale

Résumé

On a trouvé qu'un nodule sous-cutané dans un cas d'arthrite rhumatismale consistait d'un pourtour de tissu fibreux renfermant un gros amas de cristaux de cholestérol et une substance lipoïde extra-cellulaire.

La littérature concernant d'autres cas d'arthrite rhumatismale avec des nodules contenant des dépôts lipoïdes fut revisé et les résultats furent comparés avec ceux du cas mentionné.

On examina des coupes de neuf autres nodules sous-cutanés et dans huit cas la présence de grandes ou de petites quantités de substance lipoïde peut être démontrée histologiquement dans les foyers nécrotiques caractéristiques des nodules. On suggère donc que les nodules sous-cutanés de l'arthrite rhumatismale avec dépôts lipoïdes decrits antérieurement ne sont pas des entités distinctes mais qu'ils constituent seulement des produits histologiques finaux différents d'un processus ayant l'étiologie et la pathogénie communes, c.-à-d., le dépôt de la substance lipoïde dans les foyers nécrotiques des nodules.

Il semble donc qu'il n'existe aucune raison spéciale pour qu'on sépare de tels cas par une nomenclature spéciale du type ordinaire de l'arthrite rhumatismale avec des nodules contenant peu ou pas du tout de cholestérol et de substance lipoïde.

CAN THE DEFENCE MECHANISM OF THE BODY BE INFLUENCED BY ROENTGEN IRRADIATION?

REPORT ON A PRELIMINARY CLINICAL INVESTIGATION OF THE PLASMA OR SERUM PROTEIN PATTERN IN RHEUMATOID ARTHRITIS

BY

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Plan of Investigation

The profound effect on the organism of relatively small doses of *x*-rays (5 to 50 r) have been known for some time, and such small doses have been used empirically in infective and allergic conditions.

To investigate the biological properties of *x*-rays it was decided to study the possible effects of small doses of radiation on the resistance of the body, and for this purpose it was considered that patients with rheumatoid disease were suitable types. The plan decided upon was in four sections : (1) soft radiation (50 kV) to the trunk (this is mostly absorbed in the skin) ; (2) penetrating radiation (200 kV) to the trunk in the same " volume dose " as given by the soft radiation ; (3) penetrating radiation (200 kV) to the trunk of the same " surface dose " as the soft radiation ; (4) penetrating radiation locally in the same " volume dose " as in (1) and (2).

The surface dose given in (1) was decided upon with the view to the volume dose given in (3) being tolerable to the patient. It was intended to proceed in the same patient from one scheme to the others in the order given, and to note the effect both clinically and through various laboratory investigations which might provide indications of favourable or unfavourable effects of the treatment.

The following paper is an account of the first stage of the scheme, presented because of the interesting findings of evidence of the effects of the radiation used on the plasma and serum proteins, and the relation of this effect to the clinical progress of the patients.

Although no satisfactory definition of the term " natural defence mechanism of the body " can yet be given, it is generally believed that such a mechanism exists. Any functional or organic deviation from normal, whether internally or externally caused, brings into action a defending, repairing, or balancing system within the body. While little is known about the actual mechanism, it is thought that most important roles are played by the reticulo-endothelial system (R.E.S.), the liver, and the blood proteins.

In order to demonstrate the influence, if any, of wide-field irradiation with soft *x*-rays on the defence mechanism it is necessary to find some entity which is a part of this mechanism and at the same time amenable to objective observation. It has been stated in the literature (see below) that low albumin and high globulin values are frequently found in cases of rheumatoid arthritis. An investigation of these proteins was therefore begun.

It was fortunate that the first cases showed very low albumin and high globulin values, and that after the first irradiations there was a significant turn towards more normal values. This happened before any clinical signs of improvement set in ; and, thus encouraged, the tests were continued until clinical improvement could be observed. Subsequent results and the work of other investigators tend to confirm that the plasma or serum protein pattern shows a reliable correlation with at least one important part of the body's defence mechanism.

So far nine cases of rheumatoid arthritis have been treated by means of this wide-field technique, using soft *x*-rays (50 kV), H.V.L. 0·33 mm. aluminium, and doses of 5 to 50 r weekly for four to eight weeks (details are given with the charts). All patients had advanced disease that had previously failed to respond to standard treatments. In each case detailed clinical observation was combined with blood analyses of albumin, globulin, fibrinogen, erythrocyte sedimentation rate (E.S.R.), haemoglobin estimation, blood count and blood picture, before treatment and at intervals during and after the irradiation treatment. The results seem interesting enough to justify a preliminary report even though it is based on only these nine cases. Unfortunately each investigation is bound to be very lengthy and the capacity of a laboratory to handle many tests is limited.

TABLE 1

DETAILS OF NINE CASES

Case Sex Age (yrs.)	Before treatment			Best condition realized			Relapses			Intercurrent disease (no relapse in rheum. arth.)		Latest observation			Liver tests		
	Clinically*	Alb.	Glob.	Clinically	Alb.	Glob.	Clinical deterioration to	Alb. fall to	Glob. rise to	Alb. fall to	Glob. rise to	Clinically	Alb.	Glob.	Thymol turbidity	Cephalin cholesterol	Colloidal gold
1 F. 54	10.2.1948 S^{+}_{+} III 1a 2a	2·7 − − —	2·9 +(+)	S^{+}_{+} I 2	4·48 norm.	2·1 norm.				3·9 —	3·4 ++	22.12.1948 S^{+}_{+} I 2	4·3 norm.	2·5 norm.	neg.	neg.	neg.
2 F. 54	12.2.1948 S^{+}_{+} C^{+} III 1a 2b	3·0 − − —	3·2 ++	S^{+}_{+} C II 1a 2a	4·1 low norm.	2·5 norm.	S^{+}_{+} C^{+} III 1a 2a	3·4 − −	3·3 ++			5.1.1949 S^{+}_{+} C II 1a 2a	3·9 near norm.	2·7 high norm.	neg.	neg.	neg.
3 F. 45	12.2.1948 S^{+}_{+} C^{+} III 1a 2a	3·4 − −	3·2 ++	S^{+}_{+} C^{+} II 1a 2b	4·5 norm.	2·3 norm.	S^{+}_{+} C^{+} III 1a 2a	3·8 —	3·0 +(+)			14.12.1948 S^{+}_{+} C^{+} II 1a 2b	4·5 norm.	2·3 norm.	neg.	neg.	neg.
4 M. 50	29.1.1948 S_{+} III 1a 2a	3·4 — —	3·0 +(+)	S_{+} I 2	4·0 low norm.	2·4 norm.				3·4 — —	3·1 ++	5.1.1949 S_{+} I 2	4·0 low norm.	2·5 norm.	neg.	neg.	neg.
5 M. 39	12.4.1948 S^{++}_{+} C^{++}_{+} III 1a-b 2a-b	4·2 norm.	2·4 norm.	S^{++}_{+} C^{++}_{+} III 1a-b 2a-b	lower than before treat.	higher than before treat.	NO REMISSION					10.11.1948 S^{++}_{+} C^{++}_{+} III 1b 2b	3·0 — — —	3·47 ++ +	11.10.48 13 units 10.11.48 14 units congo red test negative	floccul. ++ floccul. ++	precip. + + + + precip. +++
6 F. 39	23.3.1948 S^{+}_{+} C^{+} III 1a 2b	3·9 near norm.	2·4 norm.	S^{+}_{+} C II 1a 2a	4·48 norm.	1·98 norm.	S^{+}_{+} C^{+} III 1a 2b	3·3 − −	3·2 ++			5.1.1949 S^{+}_{+} C II 1a 2a	4·0 low norm.	2·6 norm. (+)	25.10.48 4·5 units 25.11.48 4·0 units 8.12.48 4·0 units 5.1.49 5 units	neg. neg. neg. neg.	neg. precip. + precip. + neg.
7 F. 24	8.1.1948 S^{++}_{+} C^{+}_{+} III 1a-b 2a-b	2·6 − − —	3·9 + + +	S^{++}_{+} C^{+} I 1	4·5 norm.	2·4 norm.	S^{++}_{+} C^{+}_{+} III 1a 2a	3·3 − −	3·2 ++			23.12.1948 S^{++}_{+} C^{+} I 1	4·4 norm.	2·7 high norm.	neg.	neg.	neg.
8 M. 58	12.7.1948 S^{+}_{+} C^{+} III 1b 2b	3·9 near norm.	2·5 norm.	S^{+}_{+} C^{+} III 1a 2a	4·0 low norm.	higher than before treat.	S^{+}_{+} C^{+} III 1b 2a	3·8 —	3·7 + + +			4.1.1949 S^{+}_{+} C^{+} III 1a 2a	3·8 —	3·0 +(+)	22.10.48 10·5 units 24.11.48 8·0 units 4.1.49 8·0 units	C-reactive protein = slight reaction floccul. +++ floccul. + + + + floccul. +++	precip. +++ precip. +++ precip. +++
9 M. 62	9.2.1948 S^{+}_{+} C^{+}_{+} III 1a 2a	2·9 − − —	3·1 + +	S^{+}_{+} C^{+} II 1a 2a	4·7 norm.	2·5 norm.	S^{+}_{+} C^{+}_{+} III 1a 2a	4·0 low norm.	3·1 + +			30.12.1948 S^{+}_{+} C^{+}_{+} II 1b 2b	4·3 norm.	2·6 norm. (+)	neg.	neg.	neg.

* The clinical classification has been modified from Tegner's "three clinical steps"

TABLE 2
MODIFICATION OF TEGNER'S "THREE CLINICAL STEPS"
(Key to Table 1)

I	Quiescent	1. Systemically and locally quiescent.	
		2. Locally slight occasional pain, systemically quiescent.	
II	Active	1. Systemically	a : quiescent, no travelling symptoms.
			b : slight symptoms, travelling.
		2. Locally	a : occasional pain.
			b : continuous pain.
III	Very Active	1. Systemically	a : active and travelling.
			b : very active, travelling, burning.
		2. Locally	a : active, very manifest.
			b : very active, manifest, and crippling.

The material below is arranged as follows : (1) a brief account of the albumins and globulins in the blood, in normal condition and in disease ; (2) the possible aetiology and a short survey of rheumatoid arthritis ; (3) a note on soft roentgen therapy ; (4) short notes on the cases, illustrated by charts and a comparative table ; (5) a discussion of the findings ; (6) summary and conclusions.

Significance of Blood Protein Movements.—The normal ranges for the different plasma or serum proteins vary from author to author, depending on the method of investigation used and probably on the clinical material. The charts are based on the normal ranges given by Kolmer (1944).

It is important that the tests be made under the same conditions, in the same laboratory, and by the same chemist to secure standard methods as far as possible. Such a standard laboratory technique (Howe's method of salting out by Na_2SO_4) was applied. To ensure complete digestion in the Kjeldahl method selenium dioxide was used as a catalyst and digestion was continued for three and a half hours (Hoch and Marrack, 1945). It should be noticed, however, that at the beginning of the investigation the plasma proteins were used, whereas after June 1948 the serum proteins were used, in order to avoid variations arising from a water shift from the erythrocytes to the plasma, due to the oxalate used as anticoagulant.

Deviation from the normal protein pattern is unspecific, but any fluctuation of the proteins reflects the organism's changing ability to react (Wuhrmann and Wunderly, 1947, p. 144). In other words, as Stern and Reiner (1946) express it, the value of electrophoresis does not lie in the specificity of its pattern for given diseases : rather, the pattern provides information on the pathological state of the organism as a whole. There exists a close correspondence between the blood, the protein system, and the general state of health, even though there is no clear correspondence with a given pathological condition.

In rheumatoid arthritis we frequently find decrease of albumins and increase of globulins, relative or absolute, and consequently the albumin-globulin ratio is low.*

It has been found† that arrested cases of rheumatoid arthritis show a return to substantially normal albumin and globulin levels, and that treatment resulting in clinical improvement is indicated by a tendency to return to normal. Swedin and Bengtsson also observed a reduction of a previously increased fibrinogen.

Rheumatoid Arthritis.—Rheumatoid arthritis (or rheumatoid disease, a name suggested lately with very good reason by Ellman and Ball, 1948) is a systemic disease of unknown aetiology. Many workers suspect that rheumatoid arthritic patients become sensitized through some allergen and that, in fact, they are in a state of allergy in which the most obvious manifestations are pathological reactions of mesenchymal tissues. So far this is only a theory, but it is based on sound and reasonable observation and can probably explain the manifold symptoms of the disease. This theory is discussed in all modern textbooks on rheumatoid arthritis.‡

Even more various than the suspected causes of rheumatoid arthritis are the therapeutic measures which have been and are taken against the disease. Recently in his Samuel Hyde lecture Hench (1948) gave an impressive critical survey of them. General

* Wuhrmann and Wunderly, 1947, p. 276; Malmros and Blix, 1946 ; Svartz, 1943, 1944 ; Luetscher, 1947 ; Gutman, 1948 ; Loevgren, 1945.

† Gutman, 1948, p. 219; Dole and Rothbard, 1947; Swedin and Bengtsson, 1944 ; Perlmann and Kaufman, 1946 ; Malmros and Blix, 1946 ; Luetscher, 1947.

‡ Copeman, 1948 ; Comroe, 1944 ; Dawson, 1935 ; Ellman, 1947 ; Tegner, 1948 ; Loevgren, 1945 ; see also the American Rheumatism Association *Primer on Arthritis*, 1942.

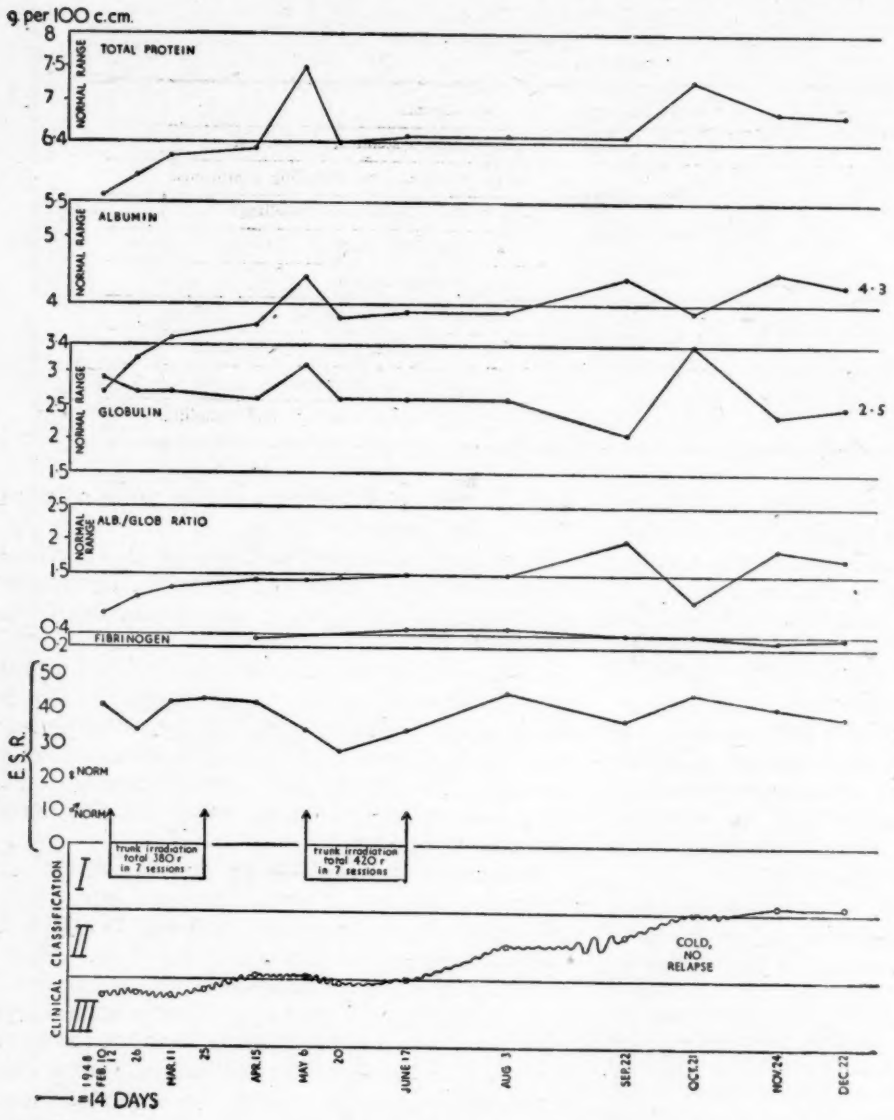

FIG. 1.—*Case 1.* A woman aged 54 years. This patient's menopause was in 1939, and rheumatoid arthritis began in 1940 ; hands (stigmatized), wrists, and knees were affected.

supporting treatment together with chrysotherapy seems to give the best results at present, but it is clear that local treatment is far less important than systemic treatment as long as the disease has not become quiescent or " burnt out ".

Soft Roentgen Therapy.—Roentgen therapy has probably been tried in every conceivable form of disease, and the immense progress with deep *x*-rays, especially in malignant disease, has completely overshadowed low-dosage, longer-wave treatment. But time and again during the last decades we find publications stressing the beneficial action of softer irradiation, especially for inflammation and for desensitization. Some authors suspected a stimulation of the body's defence mechanism. If such a beneficial influence on the systemic defence mechanism could be proved and more thoroughly explored, we might establish a most potent therapeutic agent of great importance to medicine in general.*

Whereas deep *x*-ray treatment is scientifically well founded, in spite of many theories no entirely convincing scientific proof for the mode of action of soft irradiation has been demonstrated. Even with clinical results in many cases as good, or even better, than orthodox treatment, general medical opinion

* The literature is too abundant to be mentioned in full, but fundamental work has been connected with the names of Murphy and Nakahara (1922), Scott (1939), Hernaman-Johnson (1926), Bucky (1929, 1944), Hodges (1936), Denier (1936), Medinger and Craver (1942), Holthusen (1940), Cameron (1941), Finzi (1947), Finzi and Freund (1943), Freund (1947), Kelly and Dowell (1942), and MacKee and Cipollaro (1946).

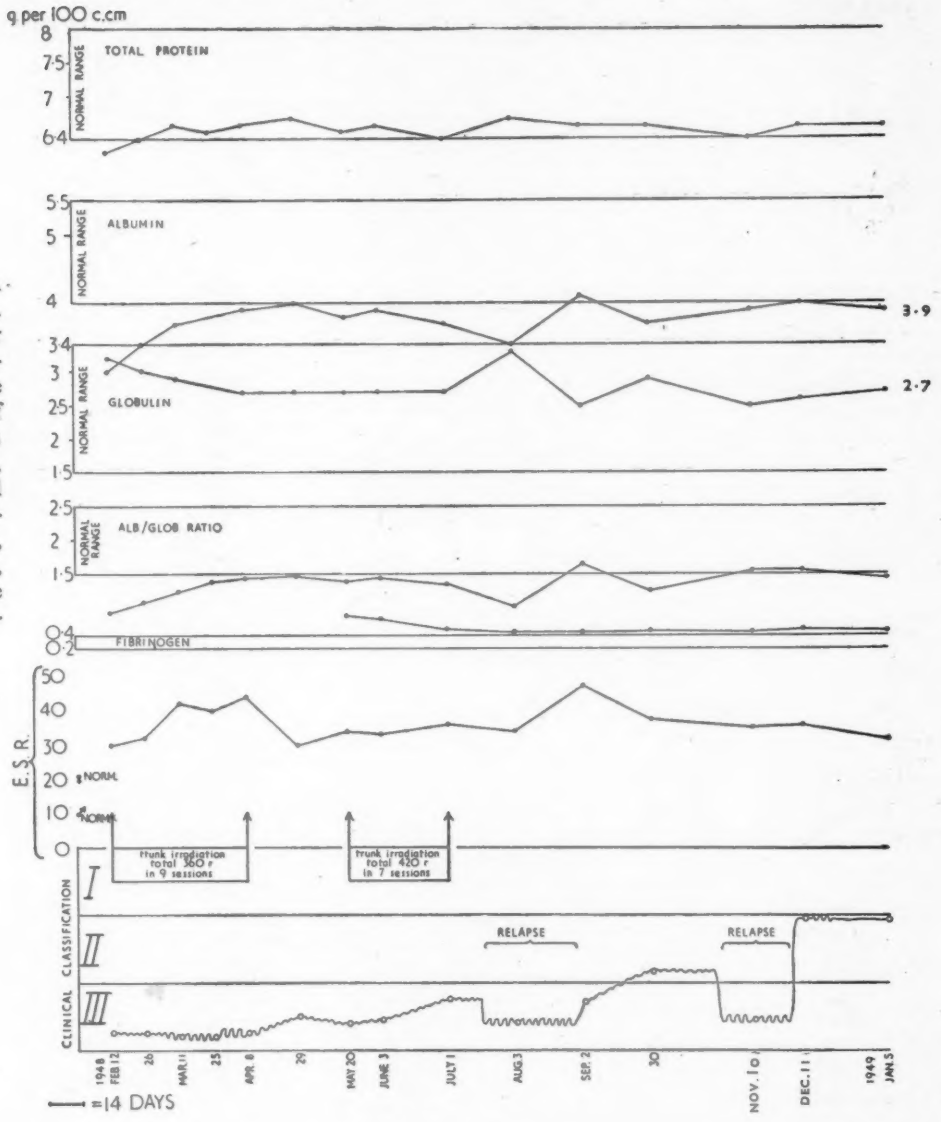

FIG. 2.—*Case 2.* A woman aged 54 years. The patient's mother was crippled with rheumatoid arthritis for the last twenty-five years of her life. The patient's menopause was in 1945, with onset of rheumatoid arthritis type polyarthritis. Hands, wrists, elbows, shoulders, neck, knees, and gait were affected. She was stigmatized and crippled.

has frowned on it as near charlatanry. The only established and acknowledged place which softer irradiation with *x*-rays has found in therapy is in dermatology. It was from experience in this branch of medicine, years ago, that the author was held by the idea that in softer *x*-ray irradiation over wide fields we may have a means of indirectly stimulating the defence mechanism of the body.

Notes on the Cases

For lack of space no detailed case histories can be given, but all essential information can be obtained from the charts and Table 1.

To assess clinical states and changes Tegner's three clinical steps have been used, modified, so as to distinguish as far as possible between systemic and local conditions. It is considered that the symptoms are essentially systemic when the patient looks toxic (pale grey to yellowish) and is of low morale, and when the symptoms are travelling, that is, switching from one place to another (although such patients have at the same time sites of predilection where local symptoms are constantly present, changing only in degree). Further it is considered a systemic symptom when the pain not only radiates into the surroundings of an affected joint, but seems also to affect the whole length of a limb or the region of a nerve. One of the very active systemic stages is described by patients as " burning " pains, often affecting the whole body. An explanation of the clinical classifications is given in Table 2. Details from case histories and results of routine tests (not contained in the charts) will be mentioned only if relevant.

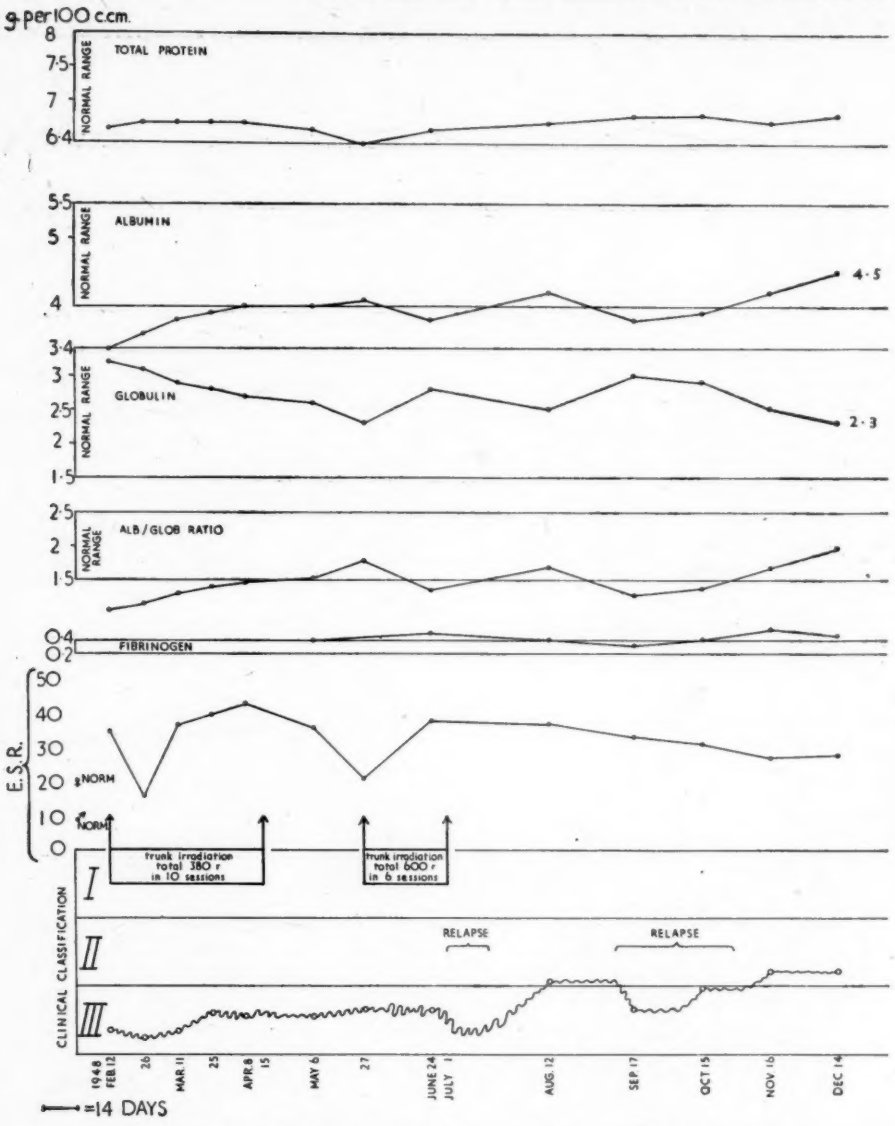

FIG. 3.—*Case 3.* A woman aged 45 years. In 1944 this patient had herpes zoster; soon afterwards rheumatoid arthritis affected her ankles, later the hands and wrists, and occasionally the sacro-iliac region. In 1946-47 she had orthopaedic treatment for flat feet. In 1947 chrysotherapy was followed by dermatitis. She was stigmatized in hands and feet, and crippled. It is difficult to judge how much of the right ankle complaint remaining is due to mechanical causes (both ankles have been manipulated, with great improvement in the left one but not in the right) and how much to rheumatoid arthritis. There are practically no pathological signs on the radiograph.

In all nine cases the wide-field treatment was carried out with a Philips Contact Therapy set : 50 kV, 0·33 mm. Al H.V.L., no added filter, 2 or 3 mA, 56 cm. f.s.d., field-trunk (30 × 50 cm.), anterior and posterior at each session (total dosage stated is the sum of anterior and posterior doses). Treatment was given once weekly, single doses varying from 5 to 50 r. The dosage may appear small, but in view of the size of the field, roughly one third of the total body surface at each session, the volume dose is not inconsiderable. It was difficult for our physicists to make an accurate estimate of the volume dose for such very soft radiation, but for the field size used they consider it to be of the order of 2,500 g.-roentgens per r at the skin.

Discussion

The difficulty in objectively assessing results due to therapeutic measures is well known in a disease with spontaneous remissions, sometimes lasting for long periods. Tegner sums up this situation very well in the short phrase : "I never discharge a rheumatoid arthritic." So far we have no means of making sure that the systemic disease has burnt out and that successful desensitization has taken place. In none of the cases described can such an ideal stage be assumed. Nevertheless Table I reveals some interesting points.

All nine patients had more or less severe, advanced rheumatoid arthritis and had gone through most forms of treatment without improvement or remissions of any length of time. Of these nine, two are considered clinical failures, and the rest have, at least for some time, made satisfactory clinical progress.

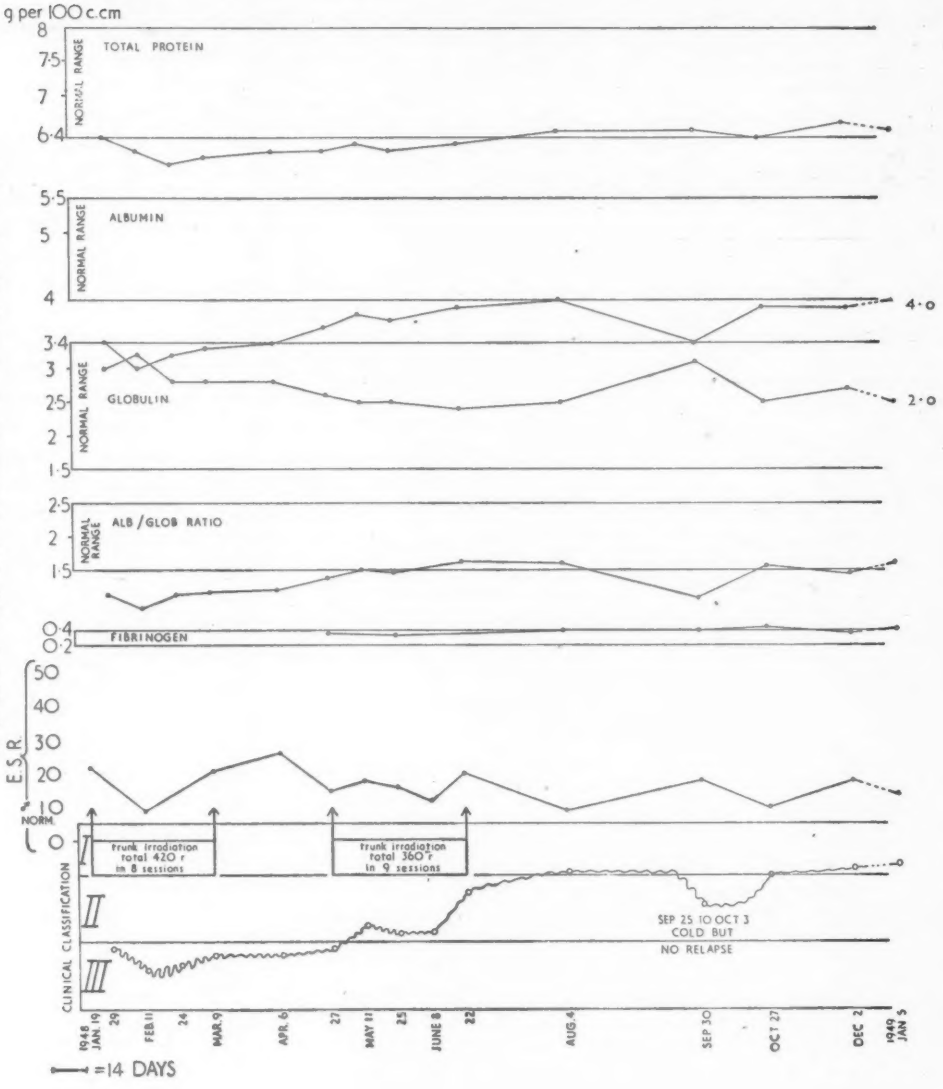

FIG 4.—*Case 4.* A woman aged 50 years. In 1944 a submaxillar lymph gland was removed (the pathological report diagnosed Hodgkin's disease, at present quiescent) followed by deep *x*-ray treatment to thorax, anterior and posterior, and neck. In 1946 he had influenza followed by rheumatoid arthritis affecting the hands (stigmatized), arms, shoulders, and occasionally the sacro-iliac region, with pain radiating to the thighs. His mother had been crippled by rheumatoid arthritis for the last twenty years of her life.

Except for variation in the severity of their rheumatoid arthritis the nine patients showed no clinical differences which would have suggested differences in their manner of response. Only in the protein pattern before treatment was there a well marked difference : the two patients who did not respond, and a borderline case showed normal globulin values, and albumin values either normal or only slightly decreased. The patients who improved had markedly decreased albumins and nearly as markedly increased globulins.

It was observed that within two or three weeks of beginning treatment the patients who improved looked better and (if they had done so before) less toxic ; the worried expression vanished and morale seemed to improve. During the first weeks the patient rarely reported any improvement in his condition ; on the contrary, sometimes there was more local pain and stiffness following a session and lasting for some hours or up to a week.

The first good sign was a report from the patient that he had had a few hours' or even days' relief from pain. Sometimes such reports were given in the latter part of a course, sometimes only some weeks after the end of the first course. It could be noticed that patients who before treatment made only slow and sparing movements made quicker and more frequent ones on improvement. In contrast to the slow clinical progress the albumins and globulins seemed to respond from the very beginning of irradiation. Improvement in the albumin and globulin curves always preceded clinical improvement.

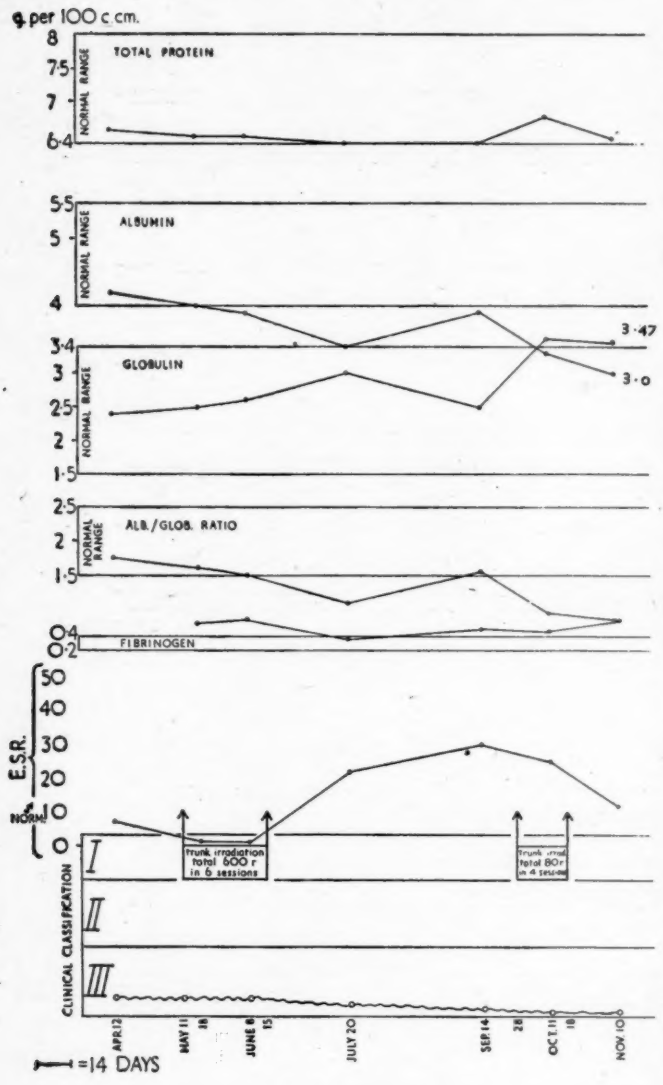

FIG 5.—*Case 5.* A man aged 39 years. The patient had psoriasis since 1929, and polyarthritis since 1945. Myochrysine produced no improvement, and the psoriasis became worse. Vaccine treatment aggravated the rheumatoid arthritis. In 1947 he had spa treatment in Bath and deep *x*-ray therapy to the spine, but without benefit. Arthrodesis was performed on the wrists and arthroplasty to the shoulders. His mother suffers from rheumatism. He himself is crippled and stigmatized in hands, arms, spine, and legs; he can hardly stand, and can walk only a few yards. The haemoglobin is estimated at 64 per cent. (100 per cent.=14·8 g. haemoglobin per 100 c.cm., error ±1 per cent.).

After a course of treatment the albumin and globulin pattern continued to improve in cases that responded well, and gradually the curves levelled out. This coincided with the consolidation in clinical improvement. After six to eight weeks' interval a second wide-field course was given, with increased dosage, but the result was generally not encouraging. In any case no consolidation could be observed of ground gained and it might have been better to wait for the further natural development.

Where relapses occurred they were preceded by unfavourable albumin-globulin readings, and a remission was foreshadowed by albumin and globulin curves making a favourable shift again. It has already been mentioned that the low albumin and high globulin pattern is similar in many other diseases (therefore it is unspecific) and only reflects the reactive power of the body. In this connexion it was observed that a shift in the wrong direction in the albumin-globulin pattern could take place without being followed by a relapse. In two such instances the patient had an acute cold, and it may well be that at the time their defence mechanism was lowered and they were more prone to relapse, even if it did not become manifest. In some of the other cases the relapse was associated with an acute cold or pharyngitis.

Case 6 must be regarded as a border line case. She was classed as not responding, but four weeks after a third course with extremely low dosage the albumins and globulins took an unexpected and favourable turn. When the blood sample was taken (Nov. 25, 1948) there was no evidence of clinical improvement, but the laboratory results obtained a few days later seemed to indicate imminent improvement. This was confirmed by the patient on Dec. 8, 1948; her right ankle was still painful and swollen, but the disease in her hands, which had been very active on Nov. 25, 1948, was now completely quiescent and her general condition had improved. The albumin and globulin values of the sample taken on Dec. 8, 1948, were still satisfactory. At the time of writing it is too early to speculate on her dubious liver function (see also below), on the state of her defence mechanism, and on whether this late remission is purely natural or can be attributed to the treatment.

It has been said that the two non-responding cases (Cases 5 and 8) showed normal globulin and near-normal albumin values before treatment. Case 5 even had a normal erythrocyte sedimentation rate (E.S.R.). With these patients the irradiation treatment had no beneficial effect on the albumin-globulin pattern, nor were their complaints relieved for any appreciable time.

The unfavourable shift in the albumin-globulin pattern can be seen clearly in Case 5. In this case it

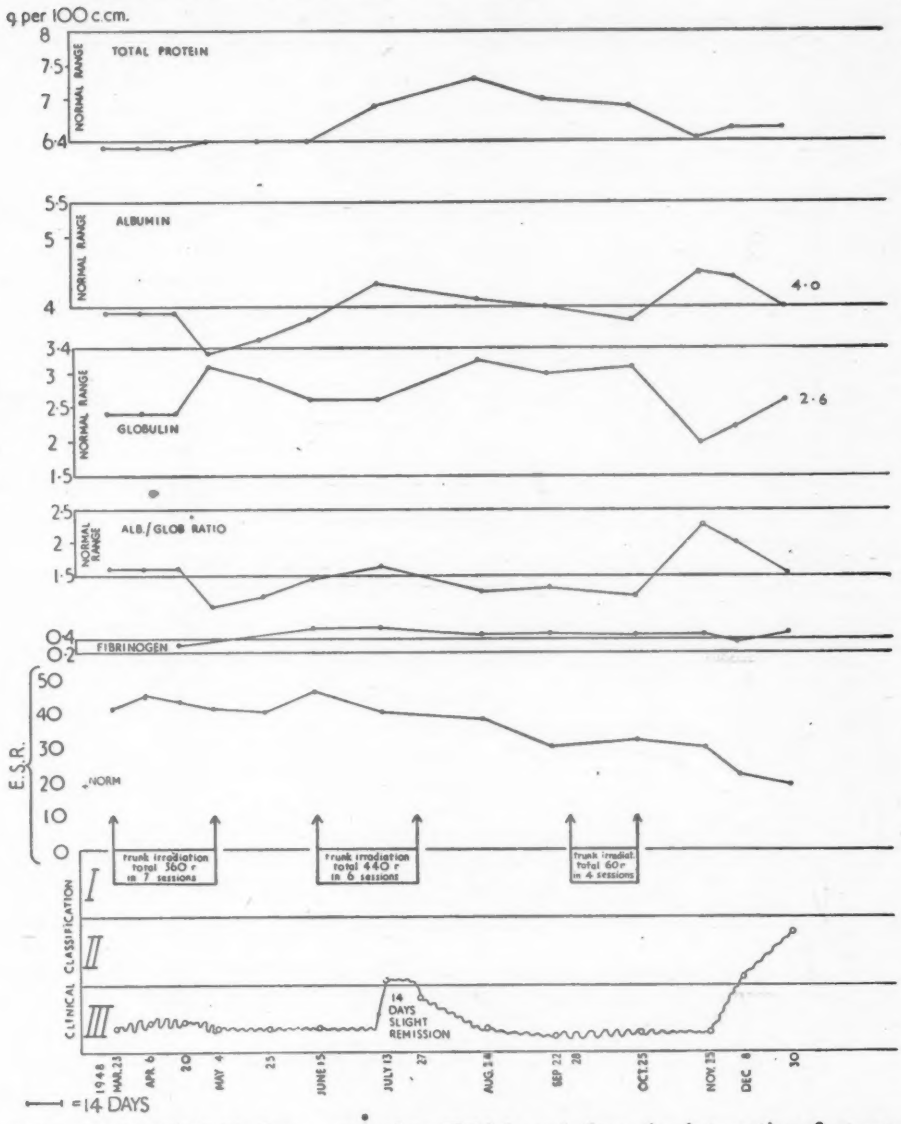

FIG. 6.—*Case 6.* A woman aged 39 years. This patient had gonorrhoea in 1936, followed by arthritis in both proximal joints of the big toes. She recovered completely (all tests concerning a possible gonorrhoeal cause in her later arthritic condition have been negative). In 1937 rheumatoid arthritis began in the left foot, and by 1938 it was in both feet and hands. In 1939 hyperthermy brought complete remission until 1943, when she relapsed. In 1943-44 there was a remission during pregnancy, and a relapse six weeks after confinement. Hands (stigmatized), wrists, elbows, knees, and ankles are affected. Her legs are crippled.

took eight weeks after the first course had finished before a slight recovery in the protein pattern took place, but there was no improvement in the patient's condition. A short trial of a second course with extremely low dosage sent the albumin curve down and the globulin curve sharply up, thus ruling out further attempts at irradiation. Case 8 showed the same development, though in a less pronounced way.

Concerning these two non-responding cases, it should be mentioned that during 1947, when a number of cases of rheumatoid diseases were being treated, liver function tests were made on each patient ; but this practice was later given up as all the tests proved negative. However, after the unfortunate experience with Case 5, liver tests were made on this patient, with positive results. All nine cases were then subjected to liver function tests (see Table) and thus the interesting fact was revealed that whereas the six responding cases showed no abnormality the two non-responding cases showed abnormality and Case 6 (the borderline case) showed a dubious result.

Can liver damage have been caused by the *x*-ray irradiation ? The dosage appears to have been far too small, fractionated, and superficial, to have caused a direct damage to the hepatic tissues. Moreover, there were no symptoms of *x*-ray sickness. It may be that through a pathological liver condition which was established before the *x*-ray irradiation,* the defence mechanism was

* It may be noted that both these patients had previously had gold treatment (Case 5 three years before, without improvement ; Case 8 from 1944 for two years, weekly, that is, for a very prolonged time, but with great improvement). Case 6 (borderline case) had had no previous chrysotherapy.

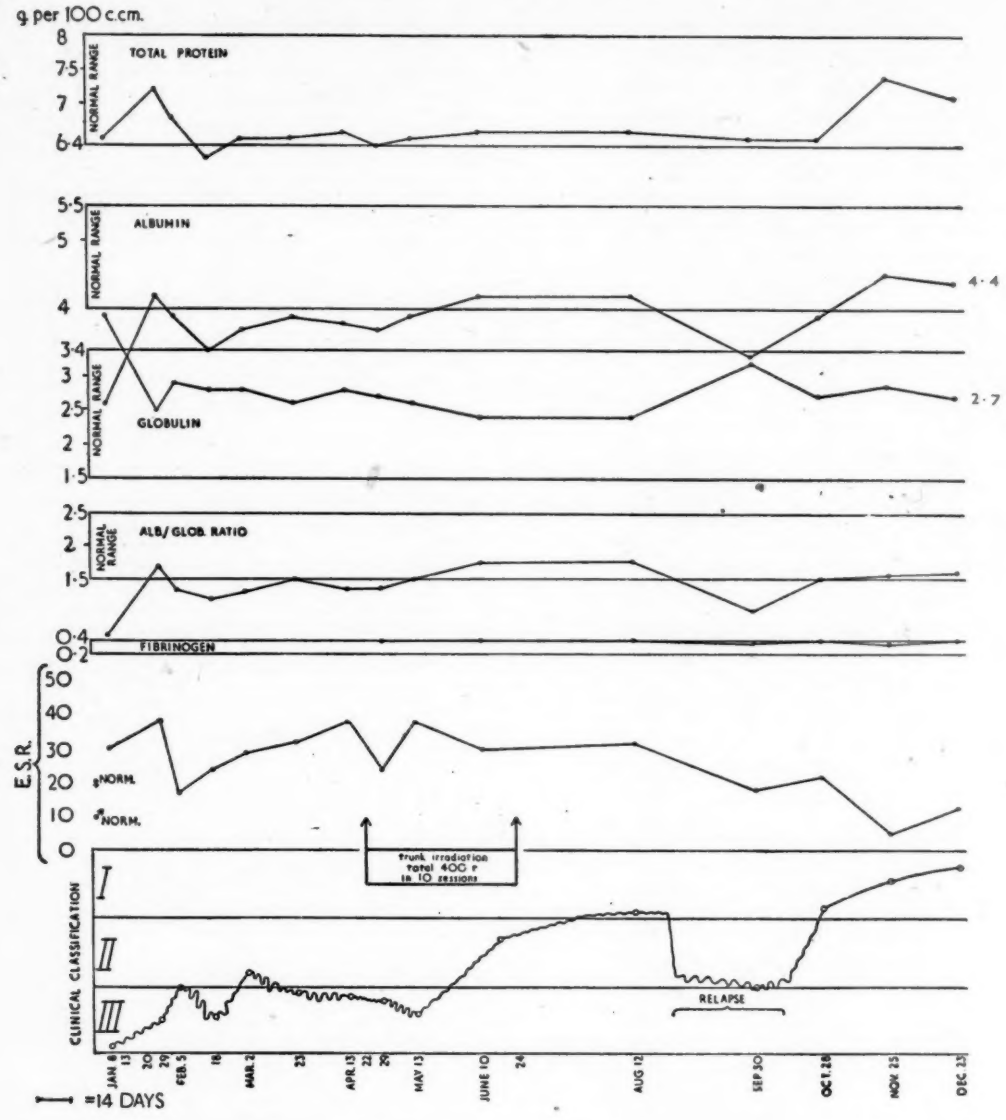

FIG. 7.—*Case 7.* A woman aged 24 years. In 1940 polyarthritis began, with remission during pregnancy and a relapse four weeks later. Her whole gait was stigmatized, and her hands were claw-like. Nearly all her joints were affected, especially hands, wrists, elbows, shoulders, spine, hips, knees, and ankles. She was very crippled.

at a low level or exhausted. The existing normal levels for albumin and globulin before treatment refer only to quantity. The question of quality will be dealt with presently. In any case there is good reason for supposing that the functional liver impairment existed even before treatment, since other authors have also drawn attention to the possibility of liver damage in rheumatoid arthritis. Loevgren (1945) suspects damage of the liver function, and he states that in ninety-three cases where necropsy had been performed 42 per cent. showed fatty degeneration of the liver, 8 per cent. amyloidosis, 10·7 per cent. cirrhosis. Wuhrmann and Wunderly (1947, p. 238) point out that the prognosis of liver damaged cases in rheumatoid arthritis is worse, since they show a strong tendency to develop fibrosis, thickening of the capsules, and ankylosis (all typical of Case 5). The same authors (pp. 204, 317) state that the most important site of manufacture and metabolism of all blood proteins is probably the liver. It is likely that the reticulo-endothelial system (R.E.S.) is the main place of formation of globulins, and as a good part of the R.E.S. is contained in the liver, damage to the latter would affect the globulins.

Unger and others (1948) report that rheumatoid arthritis and amyloidosis of the liver co-exist more frequently than is suspected. Amyloidosis was suspected in Case 5, but the Congo red test was negative. It should of course be kept in mind that

even where we do not find gross pathological changes of the liver in rheumatoid arthritis there may be cases of abnormal liver function which our present methods are not able to reveal.

With the best available methods we can still obtain only quantitative estimations ; as to the quality and functional capability of the protein fractions, we must await further discoveries. In 1938 Kendall stated that neither the albumin nor the globulin fractions are homogeneous : both fractions are mixtures of proteins which have different immunological properties. Luetscher (1947) says rightly that the increased globulin post-immunization is not necessarily identical with normal γ globulin, nor is the increase in the γ fraction entirely active antibody. When the proportions of the serum proteins are altered by disease there may be qualitative changes in the fractions and not simply more or less of the normal proteins.

Holmberg and Groenwall (1942), having the help of Tiselius himself, found a new crystalline serum globulin, not identical with any fraction of normal globulin, in a case of rheumatoid arthritis (with no signs of co-existing myeloma). Dole and Rothbard (1946) described a protein of unknown significance occurring in the serum in various diseases and contained in the α_1 globulin fraction. It is known as c-reactive protein.

Cohn and others (1946) arrived at a separation and purification of protein components which allowed some study of their individual properties and even therapeutic use.

It has been observed that hepatitis with icterus frequently has a favourable influence on rheumatoid arthritis (Hench, 1940). Loevgren (1945) found high values for citric acid and serum iron in hepatitis, and both these values are low in chronic polyarthritis, but what differences in the serum and plasma protein fractions may be present in rheumatoid arthritis and hepatitis are unknown.

Equally interesting is the not infrequent phenomenon that women with rheumatoid arthritis enjoy a remarkably complete remission during pregnancy until after term (this occurred in Cases 6 and 7). Trials with transfusion of blood of pregnant women into rheumatoid arthritics have been made (Hench, 1938 ; Barsi, 1947), but opinion is divided on the results. Normal blood transfusions have also been used. Lately Simpson and Hall Brooks (1948) reported on their investigations ; they found clinical improvement and at least a temporary return to normal albumin and globulin values.

So far functional liver impairment and a temporarily or permanently lowered (or exhausted) defence mechanism as possible causes which may influence our therapy have been mentioned, but it is quite obvious that other factors are also involved. Much may depend on the type of patient and on constitutional or acquired differences. Even if we think of rheumatoid arthritis as a manifestation

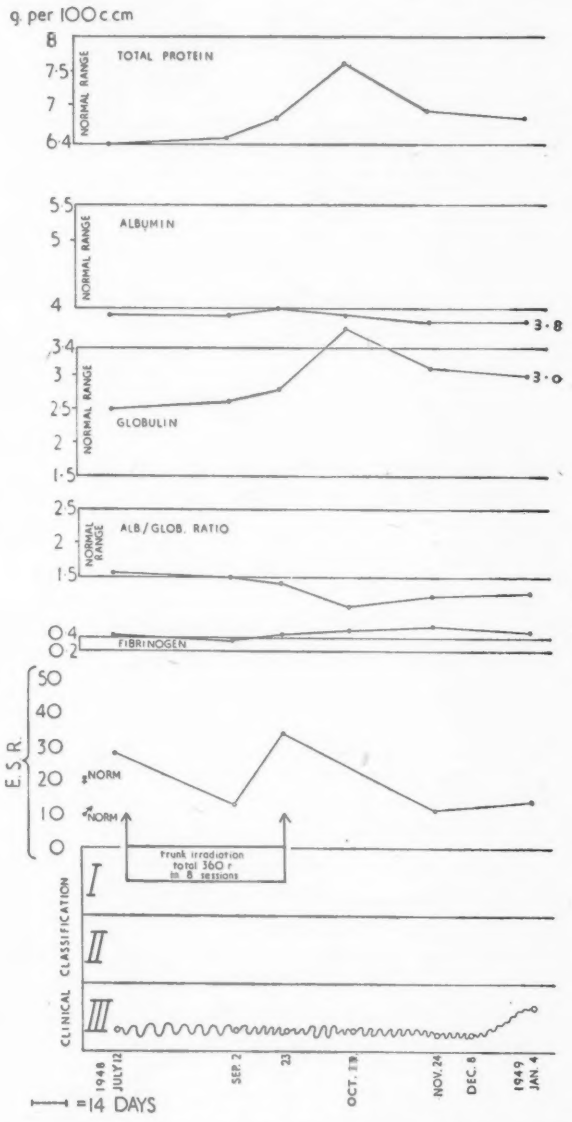

FIG 8.—*Case 8*. A man aged 58 years. Rheumatoid arthritis began in the hands in 1943 ; the patient was benefited by prolonged gold therapy (weekly injections for two years). By 1946 he could work again as a tailor. A relapse in 1947 affected the hands, arms, shoulders, spine, and legs. From January to June 1948 he had deep *x*-ray treatment to shoulders, hips, ankles, and hands, but without benefit. His hands were stigmatized and crippled.

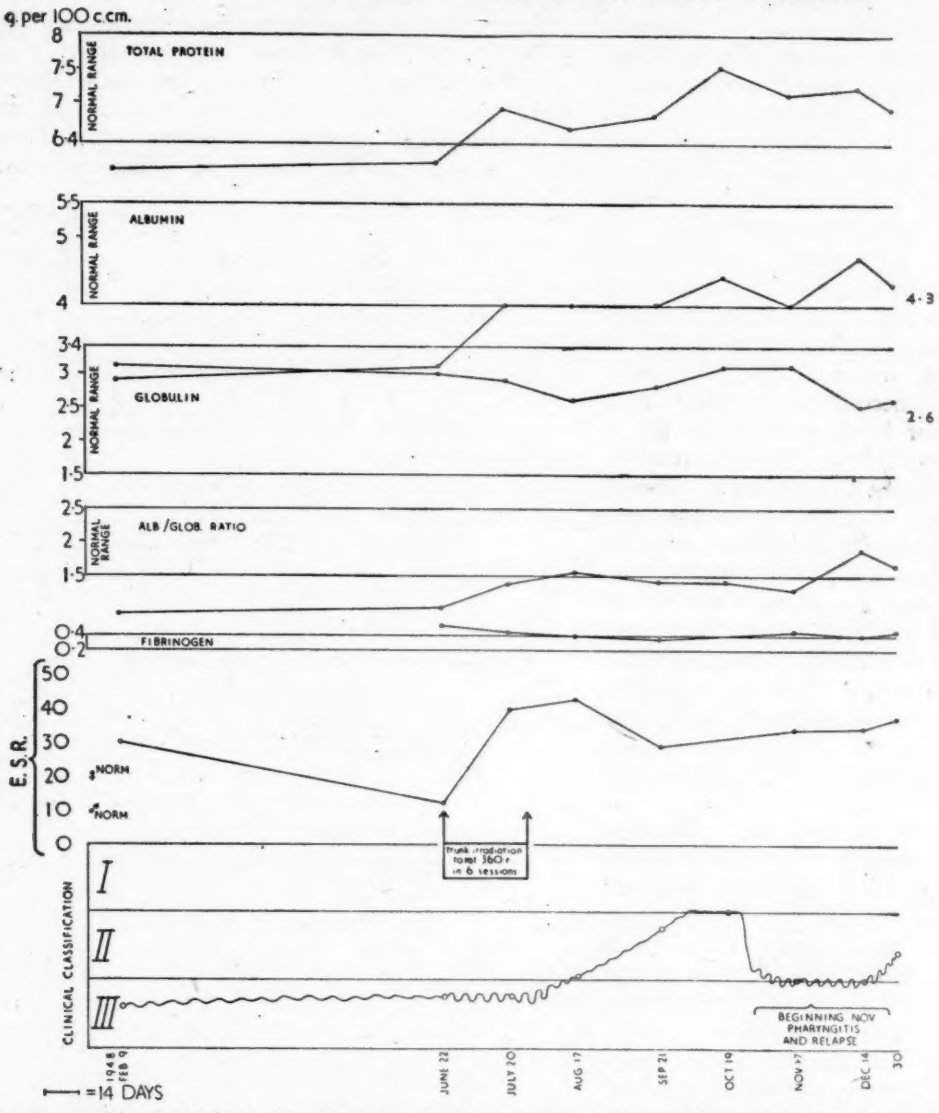

FIG. 9.—*Case 9.* A woman aged 62 years. Rheumatoid arthritis began in 1932, and the patient has had nearly continuous treatment since then, including gold and vaccine therapy, but with no improvement. Hands (stigmatized), arms, knees and walk (crippled) are particularly affected.

in a sensitized subject, we should not too readily assume that only one allergen is responsible. There may be more than one causing the same symptoms, and apparently similar cases may not yield to a similar therapy.

Many illnesses have various phases, and the phase at which treatment is given is not irrelevant. In the case of rheumatoid arthritis treated by the wide-field technique described, not only does this apply but the irradiation itself releases a biological action which probably exhibits a phase development. The correct timing of the irradiation with an appropriate dosage is therefore likely to be of utmost importance. Factors such as the quality of radiation, fractionation, and field area are no doubt important also. Clearly much more work will have to be done before approximately optimal conditions for treatment of any individual case can be assessed.

Once the aim has been realized of inducing a favourable systemic effect, possibly of desensitizing the patient, or at least of bringing about a remission, treatment by means of physical medicine or local *x*-ray application may then prove more successful than if it is given in an acute state of general manifestation of the disease.

To conclude the discussion a word must be said on fibrinogen and on the E.S.R. According to Cantarow and Trumper (1947, p. 86) a moderate increase in fibrinogen is observed in conditions causing slight hepatic injury and tissue destruction, also in pregnancy and menstruation, and following *x*-ray irradiation. In the nine cases discussed fibrinogen was found to be high ; no correlation

has been found so far with changes in the albumin and globulin pattern nor with clinical changes.

Wuhrmann and Wunderly (1947, pp. 130, 158, 163) have found that the E.S.R. depends in the first instance on fibrinogen ; also on the globulins, where an increase of any single fraction may increase the rate ; or there may be a simultaneous increase in several fractions. The accelerating effects on the E.S.R. of fibrinogen, euglobulin, pseudoglobulin, and albumin are in the ratio 100 : 20 : 2 : 1·5. Luetscher (1947), and also Malmros and Blix (1946) agree that, besides fibrinogen, a rise in any globulin fraction may cause an increased E.S.R.

In rheumatoid arthritis the E.S.R. is generally found to be increased due to higher fibrinogen and globulin values. Wuhrmann and Wunderly (1947, p. 238) found a marked persistence of a high E.S.R. in cases which were refractory to treatment.

In the present investigation no correlation between E.S.R. and changes in fibrinogen and globulin or with clinical improvement or deterioration has been found. It may be that the *x*-ray irradiation influences the E.S.R. ; it is also possible that a continuation of a raised E.S.R. during a remission in rheumatoid arthritis indicates that the systemic disease is not burnt out in spite of a return in quantity to the normal range of the albumins and globulins, the question of quality remaining open.

Unfortunately it was not possible to increase the number of laboratory tests. For a more thorough investigation it would be necessary to take more frequent readings, including several before any treatment is initiated. The serum albumin-globulin patterns should be compared with those of rheumatoid arthritics undergoing other types of treatment (especially chrysotherapy and ultra-violet light), of cases of allergy (especially bronchial asthma and industrial dermatitis, in both of which *x*-ray therapy has been successfully used), of cases of hepatitis with icterus, of pregnancy, and of cases of disease (other than rheumatoid arthritis) which show a similar low albumin and high globulin pattern. It is possible that detailed quantitative methods will reveal significant differences, especially if electrophoretic values of fractions could be made, not in sporadic single readings, but as a series. When further discoveries allow qualitative investigations we shall probably be able to make a great step forward.

Summary and Conclusions

An investigation is reported on nine cases of rheumatoid arthritis treated with wide-field, soft *x*-ray irradiation.

In all nine cases the disease was advanced and had previously failed to respond to standard treatments. The cases were all apparently similar clinically (except for degree of severity), but low serum albumins and high globulins were found in six, and nearly normal values in the other three.

Following treatment the six cases responded favourably with clinical improvement and a return of the albumin-globulin pattern to normal. Of the remaining three cases, two showed no clinical improvement and unfavourable movements in the albumin-globulin pattern ; the third (borderline case) improved belatedly and so far only for a short period, both clinically and in the protein pattern.

Functional liver tests in the six responding cases revealed no abnormality, but definite abnormality was found in the two non-responding cases and slight abnormality in the remaining case.

It is suggested that : (1) The serum albumin-globulin pattern is an unspecific but reliable indicator of the body's reactive state ; (2) soft, wide-field *x*-ray irradiation can influence a pathological albumin-globulin pattern, at least in cases of rheumatoid arthritis ; (3) a return to more normal albumin-globulin levels is followed by clinical improvement in rheumatoid arthritis ; (4) a shift in the protein pattern in the right or wrong direction foreshadows clinical improvement or deterioration : (5) an adverse shift of the albumin-globulin pattern does not necessarily signal an imminent flare-up of the rheumatoid arthritis since such a shift may be caused by an intercurrent disease, without manifestation of a relapse in the rheumatoid arthritis.

I wish to record my thanks and appreciation to Dr. F. Ellis, whose interest and encouragement enabled this work to be carried out in the radiotherapy department of the London Hospital on his and Dr. Tegner's patients ; to Prof. J. R. Marrack and Dr. W. S. Tegner for biochemical and clinical advice and valuable discussions ; to Dr. W. Shanks and Mr. R. Oliver for technical advice and help ; to Mr. M. Cohen for advice during the writing of this paper, and especially to Mr. D. V. Gharpuré who carried out all the laboratory tests in Dr. H. B. May's department at the hospital.

References

Barsi, I. (1947). *Brit. med. J.*, **2**, 252, and following correspondence.

Bucky, G. (1929). "Grenz Ray Therapy." The Macmillan Co., New York.

—— (1944). "Grenz Ray Therapy." In Glasser, O., Editor : "Medical Physics." The Year Book Publishers Inc., Chicago.

Cameron, J. A. (1941). *Radiology*, **36**, 486.

Cantarow, A., and Trumper, M. (1947). "Clinical Biochemistry." Third edit., W. B. Saunders Co., Philadelphia and London.

Cohn, E. J., Strong, L. E., Hughes, jr., W. L., Mulford, D. J., Ashworth, J. N., Melin, M., and Taylor, H. L. (1946). *J. Amer. chem. Soc.*, **68**, 459.
Comroe, B. I. (1944). "Arthritis and Allied Conditions." Third edit., H. Kimpton, London.
Copeman, W. S. C. (Editor) (1948). "Textbook of the Rheumatic Diseases." E. and S. Livingstone, Ltd., Edinburgh.
Dawson, M. H. (1935). "Chronic Arthritis." Nelson New Looseleaf-Medicine. New York.
Denier, A. (1936). *Arch. élect. méd.*, **43**, 609.
Dole, V. P., and Rothbard, S. (1947). *J. clin. Invest.*, **26**, 87.
——, —— (1946). *J. clin. Invest.* (*Proc.*), **25**, 931.
Ellman, P., and Ball, R. E. (1948). *Brit. med. J.*, **2**, 816.
—— (1947). *Proc. R. Soc. Med.*, **40**, 332.
Finzi, N. S. (1947). *Ibid.*, **40**, 115.
——, and Freund, F. (1943). *Brit. med. J.*, **1**, 34.
Freund, F. (1947). *Proc. R. Soc. Med.*, **40**, 113.
Gutman, A. B. (1948). "Plasma Protein in Disease" in "Advances in Protein Chemistry." Edit. M. L. Anson and J. T. Edsall, Vol. IV, Academic Press Inc., New York, pp. 218-9.
Hench, P. S. (1948). *Brit. med. J.*, **2**, 754.
—— (1940). *Med. Clin. N. Amer.*, **24**, 1209.
—— (1938). *Proc. Mayo Clin.*, **13**, 161.
Hernaman-Johnson, F. (1926). "Radiotherapy in Relation to General Medicine." Oxford University Press, London.
Hoch, H., and Marrack, J. R. (1945). *Brit. med. J.*, **2**, 151.
Hodges, F. M. (1936). *Amer. J. Roentgen.*, **35**, 145.
Holmberg, C. G., and Groenwall, A. (1942). *Hoppe-Seyl. Z.*, **273**, 199.
Holthusen, H. (1940). "Einführung in die Roentgenologie." G. F. Haenisch and H. Holthusen, G. Thieme, Leipzig.
Kelly, J. F., and Dowell, D. A. (1942). "Roentgen Treatment of Infections." The Year Book Publishers Inc., Chicago.
Kendall, F. E. (1938). *Cold Spring Harb. Sympos. Quant. Biol.*, **6**, 376.
Kolmer, J. A. (1944). "Clinical Diagnosis by Laboratory Examinations." First edit., D. Appleton-Century Co., New York and London, pp. 104-5.
Loevgren, O. (1945). *Acta med. scand.* (Suppl. 163).
Luetscher, jr., J. A. (1947). *Physiol. Rev.*, **27**, 621.
Mac Kee, G. M., and Cipollaro, A. C. (1946). "*X*-ray and Radium in the Treatment of Diseases of the Skin." H. Kimpton, London.
Malmros, H., and Blix, G. (1946). *Acta med. scand.* (Suppl. 170), 280.
Medinger, F. G., and Craver, L. F. (1942). *Amer. J. Roentgen.*, **48**, 651.
Murphy, J. B., and Nakahara, W. (1922). *J. exp. Med.*, **25**, 475.
——, and others (1926). *Monogr. Rockefeller Inst. med. Res.*, No. 21. New York.
Perlmann, Gertrude E., and Kaufman, Dorothy (1946). *J. clin. Invest.*, **25**, 931.
"Primer on Arthritis" (1942). American Rheumatism Association. *J. Amer. med. Ass.*, **119**, 1089.
Scott, S. Gilbert (1939). "Wide-field *X*-ray treatment." G. Newnes, Ltd., London.
Simpson, N. R. W., and Hall Brooks, D. (1948). *Proc. R. Soc. Med.*, **41**, 609.
Stern, K. G., and Reiner, Miriam (1946). *Yale J. Biol. Med.*, **19**, 67.
Svartz, N. (1943). *Nord. Med.*, **18**, 673.
—— (1944). *Ibid.*, **23**, 1713.
Swedin, B., and Bengtsson, G. (1944). *Acta med. scand.*, **119**, 426.
Tegner, W. S. (1948). *Lancet*, **1**, 469.
Unger, P. N., Zuckerbrod, M., Beck, G. J., and Steele, J. M. (1948). *Amer. J. med. Sci.*, **216**, 51.
Wuhrmann, F., and Wunderly, C. (1947). "Die Bluteiweisskörper des Menschen." B. Schwabe and Co., Basle.

Le mécanisme Défensif du Corps Humain, Peut-il être Influencé par l'Irradiation Roentgenthérapique ?

RÉSUMÉ ET CONCLUSIONS

On rapporte sur les recherches dans neuf cas d'arthrite rhumatismale traitée par des rayons *x* mous sur un champ étendu.

Dans tous les neuf cas la maladie était avancée et elle n'avait pas cédé antérieurement aux traitements classiques. Tous les cas présentaient l'apparence clinique similaire (sauf en ce qui concerne le dégré de sévérité), chez six malades toutefois on a trouvé de basses valeurs pour les albumines sériques et de hautes valeurs pour les globulines, tandis que chez les trois autres ces valeurs demeuraient presque normales.

Chez ces six malades le traitement donna des résultats favorables, comprenant une amélioration clinique et le rétablissement des valeurs normales de l'albumine et de la globuline. En ce qui concerne les trois autres malades, deux d'entre eux ne montrèrent aucune amélioration clinique et leur taux d'albumine et de globuline évolua d'une façon peu favorable ; le troisième (cas intermédiaire) fit un progrès tardif et, autant qu'on sache, de courte durée tant du point de vue clinique que sérique.

L'examen de la fonction hépatique ne revela rien d'anormal chez les six malades qui réagirent favorablement, mais une anomalie confirmée fut trouvée dans les deux cas refractaires au traitement et on observa une légère anomalie chez le troisième.

On suggère que : (1) les valeurs sériques de la globuline et de l'albumine offrent une indication non spécifique mais sure pour juger l'état réactif de l'organisme ; (2) l'irradiation étendue par des rayons *x* mous peut influencer les valeurs pathologiques de l'albumine et de la globuline, tout au moins dans des cas d'arthrite rhumatismale ; (4) un déplacement du tableau protéinique dans la bonne ou dans la mauvaise direction présage une amélioration ou une détérioration clinique ; (5) un déplacement défavorable des valeurs de l'albumine et de la globuline ne veut pas nécessairement dire qu'une aggravation de l'arthrite rhumatismale est imminente puis qu'un tel déplacement peut être causé par une maladie intercurrente, sans qu'une rechute de l'arthrite rhumatismale se manifeste.

FOCAL INFECTION IN RHEUMATOID ARTHRITIS

A COMPARISON OF THE INCIDENCE OF FOCI OF INFECTIONS IN THE UPPER RESPIRATORY TRACT IN ONE HUNDRED CASES OF RHEUMATOID ARTHRITIS AND ONE HUNDRED CONTROLS

BY

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Although the controversy regarding the aetiological role of focal infection in rheumatoid arthritis has raged for many years, no report has been found in the literature dealing with the incidence of focal infection in this disease as compared with a group of suitable controls examined under similar conditions. Accurate data on this point might be of considerable value in reaching a decision as to the importance of eradicating foci of infection in the treatment of rheumatoid arthritis. Little information is available as to the incidence of foci of infection in healthy people and in patients suffering from diseases other than rheumatoid arthritis.

Among 239 psychiatric patients, Brown (1940) discovered infection in the nose and throat in 44 per cent., in the teeth in 37 per cent., and in the urinary tract in 17 per cent. None of these patients suffered from arthritis. A large number of reports have dealt with the subject of focal infection in chronic arthritis. Cecil (1927) stated that foci of infection were present in a very high percentage of patients. The tonsils were infected in 61 per cent. of cases, the teeth in 33 per cent., and the sinuses in 15 per cent. In a later paper with Angevine (1938) it is stated that such foci are of importance in only 20 per cent. of cases and the view is expressed that they are found just as often in patients suffering from other diseases. Pemberton (1920), in a study of four hundred cases of arthritis in soldiers, found demonstrable foci in 73 per cent. In 52 per cent. the tonsils were infected, in 33 per cent. the teeth alone, and in 19·5 per cent. both teeth and tonsils. Wyatt and Bensema (1942), in a series of 343 cases of rheumatoid arthritis, discovered a focus of infection in some situation in 57 per cent. Nisenson (1941) found dental infection in 65 per cent. of 55 cases. In an analysis of 388 cases of rheumatoid arthritis, Sclater (1943) states that focal infection was present in 38 per cent. (147 cases). The tonsils were the commonest site of infection (97 cases). Snyder and others (1932) found the sinuses to be infected in 25 per cent. of 386 cases of chronic arthritis. The infection was usually of an asymptomatic or silent type. They claimed that with few exceptions the arthritis responded favourably to treatment of the diseased sinuses. Hurd (1937) laid great emphasis on the importance of infected sinuses as an aetiological cause of chronic arthritis. He stated that more than two-thirds of his series of cases had already had their tonsils removed without benefit. Treatment of the persistent sinus infection led to improvement in many cases. Bach (1947) analysed the case histories of 286 patients who sought further treatment because of active rheumatoid arthritis. Teeth had been extracted previously in 73, tonsils had been removed in 118, sinuses operated on in 7, and other foci had been dealt with in 14. Hench (1938) expressed the view that infected foci, especially oral, are probably present in 75 per cent. of people over 40 who nevertheless remain free from rheumatoid arthritis. Steindler (1934) thought that there are no tonsils in which pathological changes cannot be found after the first year of life.

No attempt has been made to present a complete review of the voluminous literature on the subject, but it will be seen that foci of infection have loomed very large in the minds of many physicians dealing with chronic arthritis. It is an undoubted fact that foci of infection are frequently found in patients suffering from rheumatoid arthritis, but their aetiological significance remains obscure. In recent years an increasing number of clinicians have adopted the view that a focus of infection is the means whereby tissues become sensitized to bacterial antigens, and that an abnormal immunological response follows any further contact with the original antigen. No satisfactory proof is available that such a sensitizing mechanism is the essential factor underlying the development of rheumatoid arthritis. If, however, it could be shown that a significantly higher incidence of focal infection is present in

patients suffering from rheumatoid arthritis than in a comparable group of controls, this would lend at least some support to the view that focal infection is of aetiological significance.

The writers accordingly felt that reliable data could best be obtained by submitting an unselected series of cases of rheumatoid arthritis to examination by an experienced ear, nose, and throat surgeon who would also examine a control series consisting of an equal number of persons not suffering from rheumatoid arthritis. Examinations were carried out in the Rheumatic Clinic, Edinburgh Royal Infirmary. Since ear, nose, and throat infections are more prevalent at certain seasons it was arranged to spread the examination of patients and controls throughout the whole of one year so that both groups would be equally affected by seasonal variations. Controls of comparable age and sex were collected from various sources. The majority were drawn from patients attending the Clinic in whom the diagnosis of rheumatoid arthritis could definitely be excluded. A number were suffering from osteo-arthritis, others from post-traumatic lesions, and in a smaller number no evidence of any organic disease could be found. The remainder consisted of patients attending the surgical or orthopaedic out-patient departments for fractures or injuries. One hundred cases of rheumatoid arthritis and one hundred controls were examined. A history of previous disease in the upper respiratory tract was noted in each case, and a swab was taken from the throat and from a tonsillar crypt. The sex and age distribution of patients and controls are shown in Table 1. There were 29 males and 71 females in each group. Seventeen of the 29 male cases of arthritis and 40 of the 71 female cases (57 per cent. of the total) were between 40 and 60 years of age.

TABLE 1

SEX AND AGE DISTRIBUTION

Age group	Rheumatoid arthritis		Controls	
	Male	Female	Male	Female
10-19	—	—	2	—
20-29	2	8	7	7
30-39	5	14	4	12
40-49	12	16	7	22
50-59	5	24	5	17
60-69	4	8	4	11
70-75	1	1	—	2
	29	71	29	71

Incidence of Septic Foci

All cases were examined impartially by the ear, nose, and throat surgeon without reference to the presence or absence of rheumatoid arthritis. Decisions as to the presence of a septic focus were taken solely upon the results of a careful examination of the upper respiratory tract of each case, and the criteria set were those which would be generally acceptable in the ear, nose, and throat department of a teaching hospital. The sinuses were radiographed in every case, but in this investigation proof-puncture was not performed where opacity of the sinuses was demonstrated. It is well recognized that sinus opacity may be due to causes other than chronic infection, and in the absence of confirmatory evidence obtained by wash-out these cases can only be regarded as having a possible sinus infection.

Rheumatoid Group

In the rheumatoid group actual or potential septic foci were discovered in 44 cases. In 37 there was a single focus, and in 7 multiple foci. Thirty-eight showed opacity of sinuses on *x*-ray examination, 11 had infected tonsils, and 4 infected lymphatic tissue in the pharynx.

In 27 cases antral wash-out only was advised. Nasal operations of a more radical nature were recommended in 5 cases because of the presence of polypi or purulent discharge. Removal of tonsils was advised in 11 cases, and in 4 others large collections of lymphatic tissue required treatment.

In cases with actual or potential foci of infection in the rheumatoid group the duration of the disease was five years or under in 29 cases, and over five years in the remaining 15. A history of previous ear, nose, or throat trouble was obtained in 27 cases, but in only 5 was there a definite time relationship to the onset of arthritis (within three months of the onset).

In 56 cases there was no clinical evidence of infection in the ears, nose, or throat. In 39 of these cases the duration of the disease was five years or under, and over five years in the remaining 17. A history of previous infection in the ears, nose, or throat was obtained in 20 cases, but in only 3 was the previous infection related to the onset of arthritis (within three months).

Amongst the 100 cases of rheumatoid arthritis, 7 gave a history of vasomotor rhinitis. In 6 cases the presence of this condition was verified by clinical examination.

Control Group

In this group potential or actual foci of infection were present in 43 cases. In 33 there was a single focus, and in 10 multiple foci. In 32 cases antral wash-out was advised, removal of tonsils in 14, and a nasal operation in 5.

A previous history of ear, nose, or throat infection was obtained in 27 cases. Three cases gave a history of vasomotor rhinitis, but none showed any clinical evidence of this condition on examination.

The data obtained from the two groups are summarized in Table 2.

TABLE 2

INCIDENCE AND SITE OF INFECTED FOCI IN ONE HUNDRED CASES OF RHEUMATOID ARTHRITIS AND ONE HUNDRED CONTROLS

	Rheumatoid arthritis	Controls
Infected foci present	44	43
Single	37	33
Multiple	7	10
Sinuses	38	32
Tonsils	11	14
Throat	4	—
Ears	—	1
Operations advised		
Antral wash-out	27	32
Nasal	5	5
Tonsillectomy	11	14
Throat	4	—

Cell Counts

Differential counts were made on stained films of the contents expressed from a tonsillar crypt in the majority of cases of both groups, but no significant information was obtained. In 75 cases of rheumatoid arthritis, leucocytes predominated in 64 and lymphocytes in 11. In 85 controls leucocytes predominated in 67 and lymphocytes in 18.

Bacteriological Examination

In each case a swab was taken from the tonsil and one from the pharynx and submitted to bacterial investigation. The predominating organisms in both groups were streptococci (haemolytic, non-haemolytic, and viridans). There was no significant bacteriological difference between the cases of rheumatoid arthritis and the controls.

Discussion

From this small investigation there appears to be no significant difference in the incidence of infected foci in the upper respiratory tract in cases of rheumatoid arthritis as compared with a group of controls of similar sex and age distribution. The incidence of focal infection, especially in tonsils, is low when compared with the figures of other investigators quoted earlier. Undoubtedly ear, nose, and throat surgeons hold widely different views as to the clinical evidence required to make a diagnosis of an infected focus. In the present investigation, where the same criteria were applied to patients and controls, the comparatively low incidence of infection in the upper respiratory tract is of less significance than the observation that there was no significant difference in the incidence in patients and in controls. The investigation was admittedly incomplete in that, where sinus infection was suggested by opacity on *x*-ray examination, the information obtained by proof puncture was not available to confirm or disprove the presence of infection. This information would undoubtedly have shown that a proportion of cases with sinuses showing opacities on *x*-ray examination were not suffering from infection in this situation. There is no reason, however, to believe that a similar finding would not have been found in the control series. All that can be said with certainty is that the incidence of abnormalities in the sinuses based on radiological examination is similar in the hundred cases of rheumatoid arthritis and in the control series. In the rheumatoid group only eight cases could recall having suffered from an infection of the upper respiratory tract within three months of the onset of the disease. The results obtained in this investigation would not suggest that infection in this situation plays a significant part in the aetiology of rheumatoid arthritis.

Summary

1. One hundred cases of rheumatoid arthritis and one hundred suitably selected controls have been investigated as to the incidence of septic foci in the upper respiratory tract.

2. Actual or potential foci were found in 44 per cent. of cases of rheumatoid arthritis and in 43 per cent. of controls.

3. Only eight patients in the rheumatoid group gave a history of an infection of the upper respiratory tract within three months of the onset of the arthritis.

4. No significant information was obtained from differential counts of the cells in material

expressed from a tonsillar crypt nor from bacteriological examination of the tonsils and pharynx which was of value in differentiating the cases of rheumatoid arthritis from the controls.

5. The results obtained do not suggest that infections of the ear, nose, or throat play an important part in the aetiology of this disease.

During this investigation one of the authors (M.S.) was in receipt of a Grant from the Empire Rheumatism Council.

References

Bach, T. F. (1947). "Arthritis and Allied Conditions." F. A. Davis Coy., Philadelphia.
Brown, C. H. (1940). *Amer. Jour. med. Sci.*, **199**, 539.
Cecil, R. L., and Archer, B. H. (1927). *Ibid.*, **173**, 258.
——, and Angevine, D. M. (1938). *Ann. int. Med.*, **12**, 577.
Hench, P. S. (1938). In Gordon, R. G.: "A Survey of the Chronic Rheumatic Diseases." Oxford University Press, London.
Hurd, L. M. (1937). *Med. Clin. N. Amer.*, **21**, 1683.
Nisenson, A. (1941). *Med. Bull. Vet. Admin.*, **18**, 57.
Pemberton, R. (1920). *Arch. int. Med.*, **25**, 231-355.
Sclater, J. G. (1943). *Annals of the Rheumatic Diseases*, **3**, 195.
Snyder, R. G., Fineman, S., and Traeger, C. (1932). *Laryngoscope*, **42**, 682.
Steindler, A. (1934). "Proceedings of the American Medical Association for the Study and Control of Rheumatic Diseases." Cleveland.
Wyatt, B. L., and Bensema, C. E. (1942). *Urol. Cutan. Rev.*, **46**, 113.

Infection Focale dans l'Arthrite Rhumatismale

Résumé

Cent cas d'arthrite rhumatismale et cent témoins convenablement choisis furent examinés en vue d'établir l'incidence des foyers septiques des voies respiratoires supérieures. Des foyers existants ou potentiels furent trouvés dans 44 pour cent des cas d'arthrite rhumatismale et dans 43 pour cent des témoins. Huit malades seulement du groupe rhumatismal présentaient une histoire d'infection des voies respiratoires supérieures endéans de trois mois précédant le début de l'arthrite.

Le compte cellulaire différentiel fait sur la substance exprimée des cryptes amygdaliennes et l'examen bactériologique des amygdales et du pharynx n'ont fourni aucun indice significatif qui permettrait de différentier entre les malades atteints d'arthrite rhumatismale et les témoins.

Les résultats obtenus ne suggèrent guère que les infections de l'oreille, du nez ou de la gorge jouent un rôle important dans l'étiologie de cette maladie.

PLASMA VISCOSITY*

BY

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The relationship between the blood sedimentation rate and plasma viscosity was first observed by Fåhreus in 1921, when investigating the mechanism of the blood sedimentation test. He did not, however, pursue the subject further, and it was not till 1940 that plasma viscosity was first suggested as a clinical test by T'ang and Wang. These workers studied a number of samples from patients suffering from pulmonary tuberculosis and concluded that plasma viscosity gave more useful information than the E.S.R. as to the activity of the disease process. About the same time Miller and Whittington (1942) were also studying the value of plasma viscosity in pulmonary tuberculosis, and their conclusions were similar. The plasma viscosity is essentially a measure of the plasma protein changes, and particularly of those proteins which are the most hydrated in colloid suspension, namely fibrinogen and euglobin (Chick, 1914). The relative importance of the individual protein changes in disease may be elucidated by means of a fractional viscosity technique.

Method

Blood is collected in an ammonium potassium oxalate† tube, and the plasma separated by centrifuging. The viscosity of the plasma is then determined. For this purpose an Ostwald viscometer was used, but any instrument of appropriate capacity is suitable. The Ostwald instrument consists essentially of two bulbs connected by a U-shaped capillary tube (Fig. 1). The plasma is sucked into the upper bulb and is then timed as it flows through the capillary tube into the lower bulb, that is from mark C to mark G. This is compared with the time taken for water. The temperature used in these tests was 25° C. The viscosity is calculated according to the formula $v=\frac{T_1}{T_2}\times 100$, where T_1 is the time taken for plasma and T_2 the time taken for water.

Having estimated the viscosity of the plasma, this is then clotted by the addition of 0·025 ml. of 40 per cent. calcium chloride for each 0·1 ml. of oxalate mixture. It is then placed in the incubator for half an hour. The clot is removed and the serum extruded from it ;

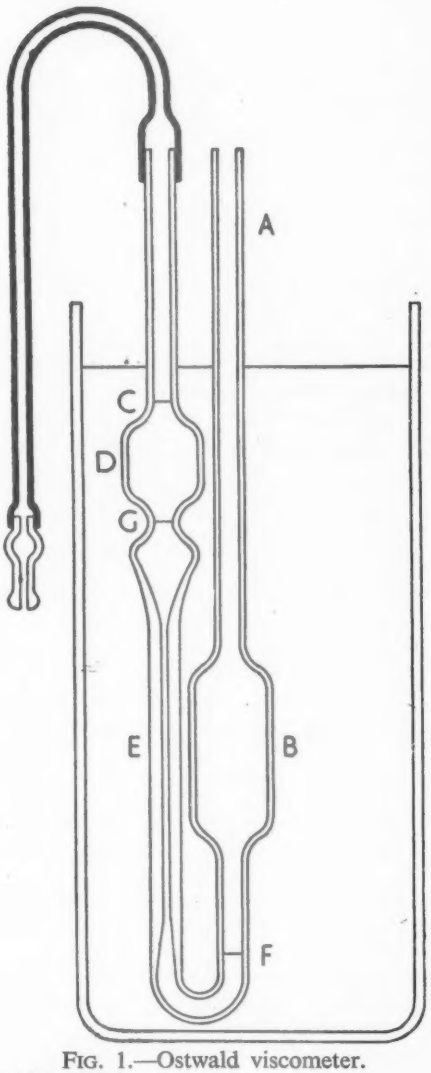

FIG. 1.—Ostwald viscometer.
A = inlet tube.
B = lower reservoir.
C = upper level of fluid at commencement of test.
D = upper reservoir.
E = capillary tube.
F = lower level of fluid at commencement of test.
G = upper level of fluid on completion of test.
The subsidiary bulb below mark G may be smaller and can be omitted altogether without serious detriment, thus reducing the amount of plasma required.

* Read at a Heberden Society meeting, Jan. 7, 1949.

† Ammonium oxalate 6 g., potassium oxalate 4 g., water to 100 ml. This solution must be kept in an incubator at 37° C. to avoid crystallization. 0·1 ml. is required for 10 ml. of blood.

the viscosity of this serum is determined. To one volume of the serum, a half volume of 4 M ammonium sulphate is then added, and the resulting globulin precipitate is filtered off. This precipitate is almost entirely gamma globulin (Jager and Nickerson, 1948). The viscosity of the filtrate is then determined and the remainder of the globulin is precipitated by the addition of a third-volume of 4 M ammonium sulphate to each volume of filtrate. The precipitate is filtered off and the viscosity of this final filtrate is estimated.

In this way four figures are obtained. An example is quoted :

	Plasma	Serum	1st filtrate	2nd filtrate	(water = 100)
Original viscosity figures	157	143	139	144	
Viscosity differences due to ammonium sulphate	—	—	16	27	
Corrected viscosity figures	157	143	123	117	

	Fibrinogen	Globulin I	Globulin II	Albumin
Fractional viscosity differences	14	20	6	17

As the filtrate contains ammonium sulphate which has an appreciable viscosity in solutions of these concentrations, a deduction must be made to allow for the viscosity of the salt solution. As the viscosity of an ammonium sulphate solution in the concentrations present in the filtrates is 116 and 127 respectively, the viscosity difference of 16 is deducted from the figure of the first filtrate and 27 from the viscosity of the second filtrate. By deducting these from the original figures a series of corrected viscosity figures are obtained. Thereafter by deducting the serum from the plasma viscosity the fibrinogen viscosity difference is calculated. In the same way by deducting the corrected viscosity of the first filtrate from the serum viscosity figure the first globulin viscosity difference is obtained, and in like manner the second globulin difference from the first and second filtrates. To convert the figure for albumin into a viscosity difference, 100, that is the value for water, must be deducted from the viscosity of the second filtrate. The method of calculation, though empirical, does in fact give figures closely similar to the published results of the viscosity of pure protein solutions, and is found to give a value approaching zero when negligible amounts of precipitate are present. There is, however, a slight error due to the effect of the salt on the viscosity of protein solutions. For example, by the addition of an increasing amount of ammonium sulphate to plasma it may be shown that up to a concentration of 1 per cent. of the salt there is a reduction of viscosity, allowing for the viscosity of the contained salt. This amounts to 1-4 in normal serum and up to 9 in pathological samples. Beyond this any further addition of ammonium sulphate does not result in a reduction of viscosity until precipitation of globulin starts at 25 per cent. saturation. The viscosity difference due to the first globulin fraction is thus made up partly of this initial salting factor, and a more accurate figure may be obtained by deducting this. In practice, however, it has been found that the introduction of this extra step into the method yields no additional information and it has therefore been abandoned.

Normal Values

Figures obtained in forty-five healthy males and females were as follows : fibrinogen 5 to 18 ; globulin I 12 to 25 ; globulin II 2 to 10 ; albumin 17 to 25.

It should be observed that these are the values obtained with the instrument described above and would not necessarily be correct for viscometers not of identical design. No significant age or sex difference was observed.

Incidence of Viscosity Changes

The incidence of the changes found in disease is shown in Table 1. The most frequent finding

TABLE 1

INCIDENCE OF FRACTIONAL VISCOSITY PATTERNS IN 213 ABNORMAL SAMPLES

	Value	%
Fibrinogen only increased	38	18
Globulin I only increased	37	17
Fibrinogen and globulin I increased	30	14
Fibrinogen and globulin II increased	12	6
Fibrinogen and globulin I and II increased	12	6
Albumin alone reduced	13	6
Globulin II only increased	10	5
Fibrinogen increased and albumin reduced	8	4
Fibrinogen and globulin I and II increased and albumin reduced	9	4
Fibrinogen and globulin II increased and albumin reduced	6	3
Globulin II increased and albumin reduced	4	2
Fibrinogen and globulin I increased and albumin reduced	4	2
Globulin II reduced	5	2
Globulin I and II increased	2	1
Globulin I reduced	2	1
Globulin I and albumin reduced	3	1
Fibrinogen increased and globulin I reduced	2	1
Globulin II increased, globulin I reduced, and albumin reduced	2	1
Globulin I and II, and albumin reduced	1	0·5
Globulin I and II increased and albumin reduced	1	0·5
Fibrinogen and globulin II increased, globulin I and albumin reduced	1	0·5
Globulin II increased, globulin I and albumin reduced	1	0·5
Globulin I increased and albumin reduced	—	0

TABLE 2

ACUTE DISEASE DURING THE FIRST WEEK

Normal	Day of disease	E.S.R. 2-15	Fib. 5-18	Glob. I 12-25	Glob. II 2-10	Alb. 17-27	Total 44-71
Bronchitis	5	9	22	26	12	18	78
Pneumonia	3	80	46	19	10	17	92
,, ...	3	65	30	13	—	—	66
,, ...	3	30	30	18	—	—	81
,, ...	4	98	45	18	—	—	94
Rheumatic fever	3	80	46	21	—	—	102
,, ,, ...	6	4	30	26	—	—	84
Salpingitis	3	13	16	14	14	22	66
Tuberculous pleurisy ..	4	32	34	23	—	—	88
,, ,, ...	3	78	40	12	—	—	86
Influenza	5	36	29	23	—	—	77
Coronary thrombosis ..	6	10	39	18	—	—	87
Erythema multiforme ..	2	86	42	19	16	17	94

TABLE 3

ACUTE DISEASE, SECOND WEEK

Normal	Day of disease	E.S.R. 2-15	Fib. 5-18	Glob. I 12-25	Glob. II 2-10	Alb. 17-27	Total 44-71
Appendicitis followed by pylephlebitis	8	49	64	34	13	21	132
Pneumonia	8	6	24	24	9	17	24
Rheumatic fever	—	50	39	27	9	24	99
,, ,, ...	12	12	28	30	—	—	87
,, ,, ...	14	46	44	32	—	—	106
Influenza	10	57	26	24	7	14	71

TABLE 4

CONVALESCENT PATIENTS

Normal	Day of disease	E.S.R. 2-15	Fib. 5-18	Glob. I 12-25	Glob. II 2-10	Alb. 17-27	Total 44-71
Lupus erythematosis (sub-acute)	120	23	17	37	6	22	82
,, ,, ,,	128	20	14	30	—	—	71
Pneumonia (acute)	21	11	16	28	9	21	74
,, ,, ...	40	9	14	26	4	21	65
Pneumonia (sub-acute) ..	90	7	18	26	4	20	68
,, ,, ..	30	13	13	29	5	22	69
Rheumatic fever	—	—	13	27	4	21	65
,, ,, with carditis	75	12	17	33	—	—	78
Tuberculous pleurisy ..	110	5	18	27	6	20	71
,, ,, ..	130	13	16	29	—	—	67

was an increase of either the fibrinogen or the first globulin fraction alone. Another common finding was an increase of both the fibrinogen and first globulin fractions, the other two remaining within normal limits. Less common was an increase of the fibrinogen and second globulin fraction or of the fibrinogen and both globulin fractions. The albumin fraction was never increased, but was not uncommonly reduced either alone or in combination with alteration in the other fractions. Only very rarely was there a reduction of the globulin fractions; the fibrinogen fraction was never found to be below the lowest normal in disease.

Significance of Viscosity Changes

At an early stage of this investigation it became apparent that the duration of the disease process was of considerable importance in determining the fractional viscosity pattern. If, for example, this is studied during the first week of disease, results are obtained as shown in Table 2.

In all but one instance the fibrinogen fraction is increased, and the second globulin fraction is increased in all instances. The first globulin fraction on the other hand is generally normal, though by the fifth and sixth days in two instances it is beginning to rise above the upper limit of normal. When the fractional viscosity is studied in the second week, the first globulin fraction is found to be raised in most cases; the fibrinogen is raised as before, but the second globulin fraction is seen to be normal in most instances (Table 3).

In convalescence, on the other hand, the fibrinogen and second globulin fractions are normal, but the first globulin fraction is raised in every instance (Table 4).

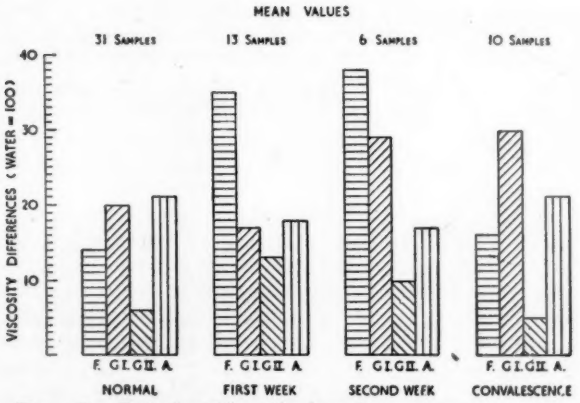

FIG. 2.—Relationship of viscosity pattern to stage of disease.

Fig. 2 shows the mean values for the differential plasma viscosity at each of these stages of disease, and emphasizes the dissociation between the fibrinogen and second globulin fraction on the one hand and the first globulin fraction on the other. This may be further illustrated by serial estimations. For this purpose changes were induced artificially by injecting T.A.B. vaccine, 28 million and then 50 million organisms, intravenously on two consecutive days into a healthy subject. In this way the sequence of events was studied in detail from the

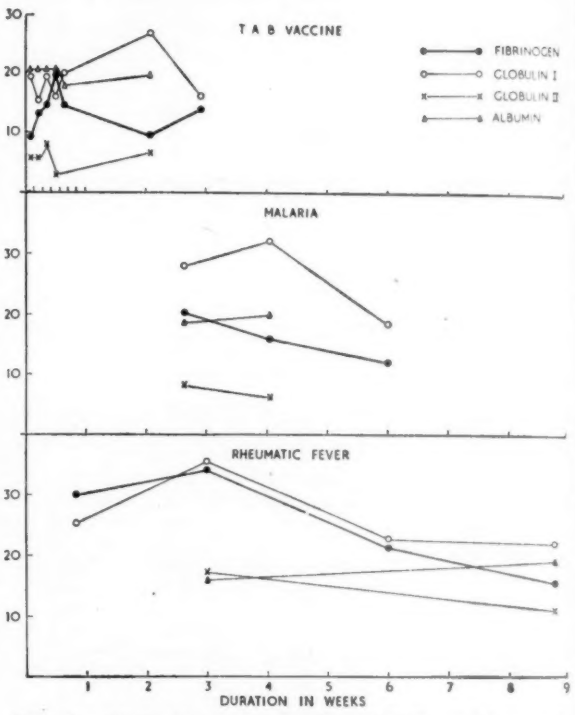

FIG. 3.—Viscosity patterns after T.A.B. vaccine and in malaria and rheumatic fever.

onset of the changes. It will be observed that the fibrinogen starts to increase on the second day, reaches a maximum on the fourth day and then rapidly subsides. The second globulin fraction runs a similar course. The first globulin fraction, on the other hand, remains normal during the first week, then rises in the second week when the others have recovered. The albumin fraction is reduced in the first week and subsequently returns to normal. The sequence suggested by the figures in Tables 2, 3, and 4 is thus confirmed.

Serial estimations have also been carried out in disease, but are necessarily less complete. In estimations during an attack of malaria (Fig. 3) the same sequence can be observed, the first globulin

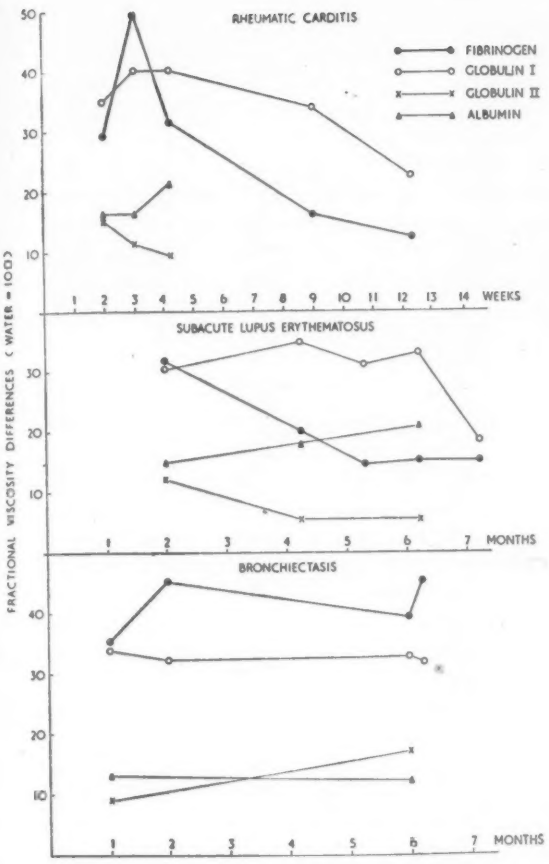

FIG. 4.—Viscosity patterns in rheumatic carditis, subacute lupus erythematosus, and bronchiectasis.

fraction rising as the fibrinogen and second globulin fraction recover. In rheumatic diseases such as rheumatic fever and rheumatoid arthritis, on the other hand, the first globulin fraction tends to be less affected and to subside more rapidly, as shown in the case of rheumatic fever in Fig. 3. Where, however, carditis supervenes, as in the case of rheumatic carditis shown in Fig. 4, a more typical first globulin response is noted, there being a lag of three weeks after the return of the fibrinogen fraction to normal. In subacute disease the changes are similar to those seen in acute cases, and this is well illustrated by the figures from subacute lupus erythematosus (Fig. 4). Here the fibrinogen response is more prolonged, normal figures being obtained only after the fifth month. The second globulin fraction as in acute disease returns to normal shortly before the fibrinogen fraction. The first globulin fraction, on the other hand, does not reach a maximum until the fourth month and then remains raised until the seventh month. The albumin in this case was not substantially reduced, but shows a steady rise synchronously with the recovery of the fibrinogen fraction.

In chronic disease one or two things may happen. There may be a continuous process as in the case of advanced bronchiectasis, shown in Fig. 4, in which the fractions maintain abnormal levels without marked variation, or there may be a recurrent process, as found for example in untreated rheumatoid arthritis or in chronic rheumatic heart disease (Fig. 5). Here the sequence already noted in acute disease recurs in cycles with or without a return to normal figures from time to time.

It should be emphasized that these changes are essentially non-specific. They are found in infections, intoxications, trauma, and ischaemia, in fact in any condition in which there is reason to suppose that tissue damage is taking place. Occasionally, however, viscosity patterns are encountered which may be of some value in diagnosis. In liver disease, for example, the typical finding is a high first globulin viscosity with little or no fibrinogen response (Fig. 6). In advanced cases both the fibrinogen and albumin fractions will be reduced. In rheumatoid arthritis the poor first globulin response has already been noted. In lymph gland disease, as for example Hodgkin's disease, lymphosarcoma, or tuberculous adenitis, the first globulin response may completely fail or this fraction may even be reduced. In renal disease, where there is marked loss of protein in the urine, the albumin and first globulin fractions are most depleted. It should be noted that the albumin and gamma globulin are fractions having the smallest molecules

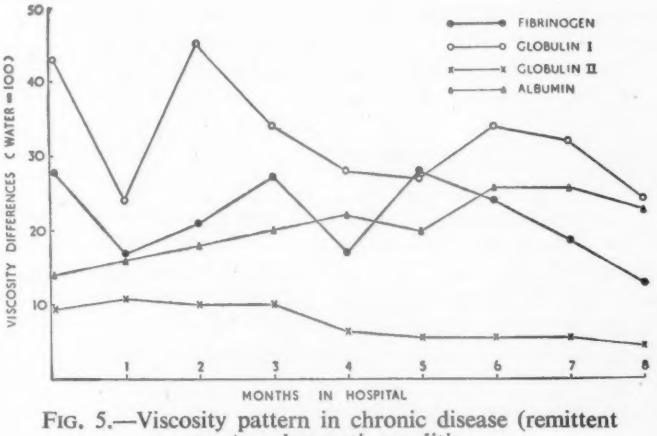

FIG. 5.—Viscosity pattern in chronic disease (remittent type) : rheumatic carditis.

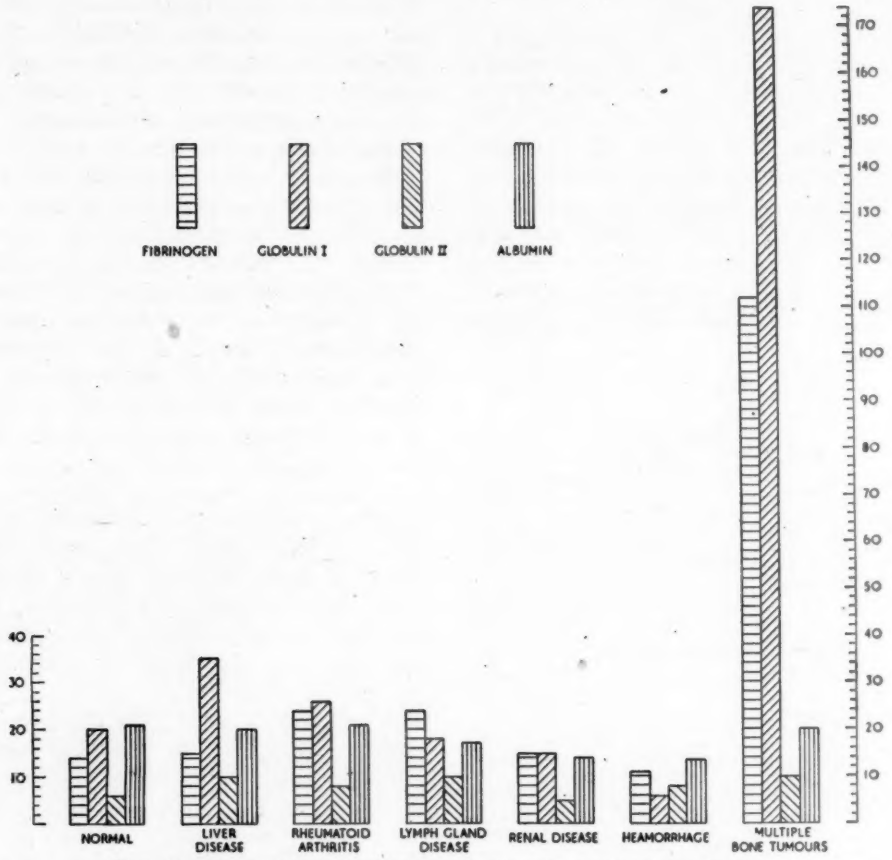

FIG. 6.—Plasma viscosity patterns in diagnosis of various diseases.

and therefore passing more rapidly through a damaged glomerulus. Following haemorrhage all fractions are reduced and the subsequent order of recovery is fibrinogen, globulin II, albumin, and globulin I. The last takes about three weeks to recover, so that it gives most useful information in the later stages of convalescence and is particularly useful when in obscure anaemia the history of haemorrhage is indefinite. On the other hand during the treatment of acute haemorrhage the fibrinogen fraction as it recovers first is most valuable. It is of interest that the changes of the first and second globulin fractions correspond closely with those noted for γ and α globulin respectively in the same diseases by Luetscher (1940 and 1941) and Malmros and Blix (1946). The most typical pattern is encountered in multiple myelomatosis, where the marked increases of fibrinogen and globulin I exceed those encountered in any other disease. Where the first globulin fraction is increased without the second, the growth is presumably a γ-globulin plasmocytoma. In β-globulin plasmocytoma it would be expected that the second globulin fraction would be affected to a relatively greater extent. Similar but less marked changes are encountered in other multiple bone tumours, particularly in carcinomatosis secondary to carcinoma of the prostate gland.

Comparison of E.S.R. and Plasma Viscosity

With regard to the comparative efficiency of the E.S.R. and plasma viscosity as an indication of abnormal changes in disease, a study of 245 cases of clinically active disease gives the following results : E.S.R. abnormal in 43 per cent. ; plasma viscosity abnormal in 59 per cent. ; fractional viscosity abnormal in 86 per cent. ; E.S.R. or fractional viscosity abnormal in 94 per cent.

Allowing for the difficulty in determining clinically the presence of active disease, these figures do indicate that, by the combined use of the blood sedimentation rate and the differential plasma viscosity, abnormality can be detected in a large

proportion of cases. It may be said with certainty that the differential plasma viscosity is never normal in the presence of gross disease, and that where no change is found in either the E.S.R. or differential viscosity any disease present is either very mild or localized. There is one exception to this, namely disease of the central nervous system or of the meninges, in which gross pathology may be present with negligible changes in the blood. In such disease processes, examination of the cerebrospinal fluid gives more reliable information.

Summary

A method is described for studying the factors concerned in the viscosity of the plasma. This method, which has been termed the differential plasma viscosity, provides a simple means of determining the relative changes of the plasma protein fractions, particularly the fibrinogen and γ globulin. A series of plasma samples from healthy individuals and from patients suffering from a wide variety of disease processes were studied by this method.

The results of this study indicate that the changes in disease depend more on the stage than on the nature of the process. During the early stages the fibrinogen and second globulin fraction (presumably α globulin) are increased but the first globulin fraction (γ globulin) remains normal. In the second week the first globulin fraction also increases. In convalescence the first globulin fraction remains raised for a time after the other fractions have returned to normal. The albumin fraction is reduced in the early stages in a proportion of cases. The actual duration of these changes depends on the acuity of the disease. In a transient process the lag between the first globulin fraction on the one hand and the fibrinogen and second globulin fractions on the other, may be a matter only of a week ; in a subacute disorder it may be a month or two. In chronic disorders there may be a constantly altered level of all fractions or a remittent course may be followed. In the latter, the sequence of changes noted in acute disorders may be observed to recur with each relapse.

Following haemorrhage the same sequence may be observed but in reverse. All fractions are at first reduced. The fibrinogen fraction recovers most rapidly, generally within twenty-four hours of cessation of the haemorrhage, and this is followed by the second globulin fraction, the albumin and lastly the first globulin fraction, which may take three weeks to return to normal.

Certain characteristic patterns in disease are noted : the poor globulin I response of rheumatoid arthritis ; the absent response of this fraction in widespread lymph gland disease ; the high globulin I response of liver disease ; and the very high values for both fibrinogen and one of the globulin fractions in multiple tumours of bone, particularly multiple myelomatosis.

Comparison of the differential plasma viscosity with the E.S.R. and the simple plasma viscosity indicates that the first is a more sensitive indicator of pathological plasma protein changes than either of the other two and that the E.S.R. is the least reliable. It is recommended that both the E.S.R. and the differential plasma viscosity be used in doubtful cases.

References

Chick, H. (1914). *Biochem. J.*, **8**, 261.
Fåhreus, R. (1921). *Acta med. scand.*, **55**, 1.
Jager, B. V., and Nickerson, M. (1948). *J. clin. Invest.*, **27**, 231.
Luetscher, J. A. (1940). *J. clin. Invest.*, **19**, 313.
—— (1941). *Ibid.*, **20**, 99.
Malmros, H., and Blix, G. (1946). *Acta med. scand.*, Suppl. 170, p. 280.
Miller, A. K., and Whittington, R. B. (1942). *Lancet*, **2**, 510.
T'ang, B. H. Y., and Wang, S. H. (1940). *Chinese med. J.*, **57**, 546.

Viscosité du Plasma

Résumé

On décrit une méthode pour étudier les facteurs impliqués dans la viscosité du plasma. Cette méthode, qui reçut le nom de viscosité différentielle du plasma, fournit un moyen simple pour déterminer les modifications relatives des fractions protéïniques du plasma, particulièrement du fibrinogène et de la γ globuline. On a étudié par cette méthode une série d'échantillons de plasma des sujets sains et des malades souffrant d'une grande variété de processus morbides.

Les résultats de cette étude indiquent que les changes morbides dépendent plus du stade du processus que de sa nature. Au stade initial le fibrinogène et la seconde fraction de la globuline (probablement la globuline α) se trouvent augmentés, mais la première fraction (globuline γ) demeure normale. Au cours de la deuxième semaine la première fraction de la globuline augmente également. Pendant la convalescence la première fraction de la globuline demeure augmentée pendant un certain temps après que les autres fractions aient récupéré leur valeur normale. La fraction albumine est diminuée pendant la période initiale dans un certain nombre des cas. Dans les processus passagers le décalage entre la première fraction de la globuline d'un coté, et le fibrinogène et la seconde fraction de la globuline de l'autre, peut durer seulement une semaine ; dans un trouble subaigu il peut persister un ou deux mois. Dans les troubles chroniques les valeurs pour toutes les fractions peuvent se trouver

à un niveau modifié ou bien elles peuvent avoir une évolution rémittente. Dans ce dernier cas la succession des changes observés dans les troubles aigus peut se répéter au cours de chaque rechute.

Après une hémorragie on peut voir la même séquence, mais à l'envers. Toutes les fractions se trouvent d'abord diminuées. Le fibrinogène se relève le plus rapidement, généralement endéans de vingt-quatre heures qui suivent l'arrêt de l'hémorragie ; il est suivi de la deuxième fraction de la globuline, de l'albumine et, finalement, de la première fraction de la globuline ; le tout redevient normal au bout de trois semaines.

On note certains types caractéristiques de la maladie : la faible réponse de la globuline I dans l'arthrite rhumatismale ; l'absence de sa réponse dans l'affection étendue des ganglions lymphatiques ; sa forte réponse dan les maladies du foie ; et de très fortes valeurs pour le fibrinogène et pour une des fractions de la globuline dans les tumeurs multiples des os, en particulier dans la myélomatose multiple.

L'étude comparée de la viscosité différentielle du plasma, de la sédimentation globulaire et de la simple viscosité du plasma montre que la première costitue la méthode la plus sensible pour se rendre compte des changes pathologiques de la protéïne du plasma et que la sédimentation globulaire est un indice moins constant. On propose l'emploi de la sédimentation globulaire et de la viscosité différentielle dans les cas douteux.

EARLY SYMPTOMS OF RHEUMATOID ARTHRITIS

BY

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The opinion has been held in many quarters (e.g. Freund, 1929 ; Nyfeldt, 1944) that rheumatoid arthritis most often sets in insidiously and gradually. Kahlmeter (1944) considers it a characteristic feature of rheumatoid arthritis that it has " a predilection for small joints " and that the joint symptoms have a tendency to spread from peripheral joints and centripetally. Nevertheless, there are cases of rheumatoid arthritis that have an acute onset. According to this author, difficulty in differential diagnosis hardly exists.

Like Kahlmeter, many people distinguish between two forms of rheumatoid arthritis : one, as described by Charcot, with insidious onset, symmetrical joint symptoms, and low temperature ; and another with more acute onset, febrile reaction, and joint symptoms setting in violently. In British literature especially there are to be found these two types of rheumatoid arthritis under the respective designations of rheumatoid arthritis and infective arthritis. The terms " typical " or " primary " and " atypical " or " secondary " chronic are also not uncommon.

Comroe (1944) says that approximately 15 per cent. of the cases do not display the typical, insidious, and creeping start with symmetrical joint symptoms. In some 5 per cent. of cases the rheumatoid arthritis may be " atypical " for several months. These " atypical " cases may at times display symptoms in only one joint. Kinsella (1942) considers that when the disease sets in after the age of 50 it is acute at the outset and with a more rapid course and better prognosis. Ropes and Bauer (1945, cited by Hench and others, 1948) distinguish several types of (chronic) atypical rheumatoid arthritis : (1) with asymmetrical involvement, often a monarthritis ; (2) with sudden febrile onsets precipitated by acute infection and accompanied by skin rash and migratory joint involvement ; (3) bouts of arthritis precipitated by respiratory or other infections and not followed by permanent articular residues ; (4) with febrile onset resembling rheumatic fever (common among soldiers) ; (5) with transient swellings affecting one joint and then another, resembling " palindromic syndrome " ; (6) having recurrent joint and muscle aching and stiffness with qualitative characteristics of so-called " primary fibrositis ".

According to Ropes (1944a, b), typical advanced (chronic) rheumatoid arthritis presents little difficulty in diagnosis, but the so-called " atypical " forms are so common that it may be asked whether the " common " picture with insidious start, slowly progressing course, and symmetrical joint symptoms should be regarded as being the typical. Borman (1945), and Ropes and Bauer (1945) also point out the diagnostic difficulty in the " pre-arthritic " stage of rheumatoid arthritis.

The Present Investigation

We have long been interested in these questions and have gone through the records of two hundred patients with particular attention to early symptoms. All the cases were treated in Med. Dep. III of Södersjukhuset in recent years. Only cases of true rheumatoid arthritis have been considered.

We have distinguished the following types :

Type 1 is characterized by a slow and insidious onset and progressing course ; there is no fever, at least to begin with. The joints first involved are those of the peripheral extremities, and progress is centripetal and symmetrical.

Type 2 is characterized by an acute onset involving small joints. Sometimes there is fever, and in such cases the disease is clinically extremely reminiscent of rheumatic fever.

Type 3 is similar to type 2 except that the large joints are the first affected. The similarity to rheumatic fever is thus even more striking. It may be disputed whether one should and can make a distinction between types 2 and 3, or whether these two groups should rather be merged in one.

Type 4 consists of cases where the joint symptoms are mainly confined to hands and feet for considerable periods. The joint symptoms are asymmetrical, and although they may be pronounced the skin symptoms and muscle atrophy are not. The

sedimentation rate is low, and the tendency to progress relatively slight. This type of rheumatoid arthritis has been described by one of us (Jonsson) under the name of "atypical rheumatoid arthritis".

Type 5 starts with arthralgic symptoms: pain in joints without apparent objective joint changes. Arthralgia is often localized in the hands and may continue for long periods before objective symptoms appear.

Type 6 covers the remaining cases. In these the symptoms start in large or small joints, with or without fever. There is less symmetry, and in general the joint symptoms are difficult to characterize or classify. Extra-articular symptoms may occur.

We have distinguished a separate group of cases with the same division as the above, but with the difference that the course at the beginning was intermittent, so that there were periods without trouble alternating with periods when symptoms were present.

Our results are summarized in the Table. What impresses one most in looking at this table is that type 1, the so-to-speak "classical", slowly progressing rheumatoid arthritis type with symmetrical joint symptoms, did not occur in more than 37·5 per cent., that is, in a little more than one third of the cases, whereas the types 2, 3, and 6 comprised 51·5 per cent. Even if the type 2 be subtracted, which of course is difficult to distinguish from type 1 as the joint symptoms in both groups start in small joints, we get the figure of 44·5 per cent., or nearly half.

The fact that type 4—the "atypical"—does not occur to the extent of more than 1 per cent. should not be any surprise. More striking, however, is that the cases starting with arthralgic symptoms are common enough to make 10 per cent. of the total. This illustrates the importance, even in cases of pain in the joint without demonstrable objective changes, of keeping the diagnosis of rheumatoid arthritis in mind. The Table also shows that the preponderance of women, noticeable in all groups, is particularly striking in this one.

Cases of type 6 represent no less than 30 per cent. As stated above, the joint symptoms here are in general difficult to characterize or classify. Even extra-articular symptoms occur, so that in these cases the clinical picture at the start of the disease may simulate, for example, peritendinitis calcarea, a stiff shoulder, a defect of the feet, etc. Symptoms may start in any joint.

From the Table it will be seen that the cases with intermittent symptoms are rather less common in type 1 than in the other types. As regards age of onset, the different types are the same.

Our material shows that early rheumatoid arthritis can be present in many forms and that the slow progressing type, which might be thought characteristic of rheumatoid arthritis, does not in fact occur as often as is sometimes supposed (compare Rope's statement above). We consider it justifiable to suspect early rheumatoid arthritis even when the symptoms are relatively uncharacteristic.

Summary

Material from two hundred cases of rheumatoid arthritis has been collected. On the basis of the mode of onset, six types are distinguished. Type 1 starts insidiously, with symmetrical joint symptoms beginning

TABLE

ANALYSIS OF CASES OF RHEUMATOID ARTHRITIS ACCORDING TO TYPE

	1. Slow, progressing symmetrical symptoms		2. Acute start in small joints		3. Acute start in large joints		4. "Atypical" benign cases, hand and foot		5. Arthralgia symptoms		6. Uncharacteristic symptoms	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
Continuous symptoms ..	10	54	5	4	4	1	—	1	1	7	11	32
Intermittent symptoms ..	4	7	1	4	3	9	—	1	1	11	5	24
Total cases ..	14	61	6	8	7	10	—	2	2	18	16	56
	75		14		17		2		20		72	
Percentage ..	37·5		7		8·5		1		10		36	

in the peripheral joints and progressing centripetally. Type 2 starts as acute in the small joints, possibly with fever. Type 3 is like type 2 except that the joint symptoms begin in the large joints. The resemblance to rheumatic fever is striking. Type 4 consists of benign cases with asymmetrical joint symptoms and low sedimentation rate. Type 5 starts with arthralgic symptoms. Type 6 covers the remaining cases. The symptoms start in large or small joints with or without fever, and the symmetry is not particularly pronounced. Extra-articular symptoms may occur.

Type 1 occurs in only 37·5 per cent., types 2, 3, and 6 in not less than 51·5 per cent. of the cases. Type 6 occurs in 36 per cent. and type 5 in 10 per cent. The investigation shows that early rheumatoid arthritis may have a varied picture. One is justified in suspecting early rheumatoid arthritis even when the symptoms are relatively uncharacteristic.

References

Borman, M. C. (1945). *Wisc. Med. J.*, **64**, 684.

Comroe, B. I. (1944). "Arthritis and Allied Conditions." London.

Freund, E. (1929). "Gelenkerkrankungen." Vienna.

Hench, P. S., and others (1948). *Ann. int. Med.*, **28**, 66.

Jonsson, E. (1946). *Nord. Med.*, **29**, 189.

Kahlmeter, G. (1944). "Nordisk Laerebog i intern Medicin. II." Copenhagen.

Kinsella, R. A. Cit. from Hench and others (1948). *Ann. int. Med.*, **28**, 66.

Nyfeldt, A. (1944). "Forelaesninger over de rheumatiske Ledsygdomme." Copenhagen.

Ropes, M. W. (1944a). *Bull. New Engl. Med. Center.*, **6**, 54.

—— (1944b). *Arch. Phys. Therapy*, **25**, 397.

——, and Bauer, W. (1945). *New Engl. J. Med.*, **233**, 592, 618.

Symptômes du Début de l'Arthrite Rhumatismale

Résumé

Des données concernant deux cent cas d'arthrite rhumatismale furent recueillies. En se basant sur le mode de début, on en distingue six types. Le type 1 commence d'une manière insidueuse, avec des symptômes articulaires symétriques débutant aux articulations périphériques et progressant vers le centre. Le type 2 commence d'une manière aiguë aux petites articulations, quelquefois avec de la fièvre. Le type 3 ressemble au type 2 sauf que les symptomes articulaires commencent aux grandes articulations. La ressemblance au rhumatisme articulaire aigu est frappante. Le type 4 comprend les cas benins avec des signes articulaires asymétriques et la sédimentation globulaire basse. Le type 5 débute par des symptômes arthralgiques. Le type 6 couvre les cas restants. Les symptômes apparaissent dans les articulations grandes ou petites, avec ou sans fièvre, et la symétrie n'est pas particulièrement prononcée. Des symptômes extra-articulaires peuvent se présenter.

Le type 1 se présente seulement dans 37·5 pour cent des cas, les types 2, 3 et 6 dans pas moins de 51·5 pour cent. Le type 6 se présente dans 36 pour cent et le type 5 dans 10 pour cent des cas. L'investigation montre que l'arthrite rhumatismale du début peut présenter un tableau variable. On a le droit de soupçonner le début d'une arthrite rhumatismale même si, relativement, les symptômes ne sont pas caractéristiques.

CERVICAL SYMPATHETIC BLOCK IN PERIARTHROSIS OF THE SHOULDER JOINT WITH SECONDARY REFLEX DYSTROPHY

BY

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Periarthrosis humeroscapularis with restricted mobility of the shoulder joint is in some cases accompanied by changes in the hand on the same side (shoulder-hand syndrome). In advanced cases the hand is slightly cyanotic and damp, and there is stiffness and swelling of the fingers and hand, mostly in the morning ; there may be pain and varying degrees of perspiration ; the skin of fingers and palms may be drawn tight so that the lines of the hand are effaced. The appearance is very much like that of post-traumatic reflex dystrophy, both in the violence of the pain and in the capricious way in which some persons are attacked by reflex dystrophy, others not. Still later in the disease fibrous nodes or strings may appear in the subcutaneous tissue in the palm of the hand or in the interstices, and osteo-arthrosis may in rare cases appear in the interphalangeal joints.

The fibrous changes may virtually diminish in most cases, even though there may still be some nodes or tightness hindering the full spreading of the fingers and causing lasting disablement. The changes in the soft tissues of the hand and fingers are of the same hard character as the changes in the soft tissues around the affected shoulder joint.

The aspect of the hand, the resemblance to the post-traumatic reflex dystrophy, and the course of the disease, makes one suspect that the sympathetic nervous system is involved ; both Kahlmeter (1936) and others have had the same idea, and as post-traumatic reflex dystrophy can be improved or cured by sympathectomy, it seems that it is worth paying attention to the sympathetic nervous system in cases of periarthrosis humeroscapularis simulating reflex dystrophy. One might hope (1) to avoid further development of restricted mobility of the shoulder joint ; (2) to avoid further development of stiffness of hand and fingers ; (3) to soften the leathery, dry hand in old cases of reflex dystrophy ; and (4) to eliminate pain.

Treatment

In 1944 two patients with periarthrosis humeroscapularis were treated under my direction by stellate ganglion block. One of them had about ten blocks without any definite effect. The other one had one single block which was completely without effect. The technique used at the time seemed to me so difficult that I found it impracticable to perform it to any greater extent on ambulant patients.

At the rheumatological congress in Copenhagen in 1947, Otto Steinbrocker from New York presented a report on six cases of periarthrosis humeroscapularis with secondary reflex dystrophy treated by stellate ganglion block and block of the brachial plexus. Dr. C. Gillmor, Kansas City, was kind enough to demonstrate to me the technique applied, and he informed me at the same time that Dr. Steinbrocker and he in most cases only used stellate ganglion block, and that one injection was, in their opinion, often sufficient.

Method.—The injection is made in the following manner. The patient lies on his back with a pillow under his neck and the upper part of the back, so that the head is bent backwards. The cricoid cartilage is palpated, and its lower edge and the medial border of the m. sternocleidomastoid are marked with iodine cotton. The needle (Rowika 80 × 100) is introduced along the lower edge of the cricoid cartilage just between the medial border of the sternocleidomastoid and the centre line of the neck, so that the introduction is made between the trachea and the carotid artery, directly above the glandula thyroidea. The needle is introduced until it touches the periosteum on the cervical vertebra, and 10 c.cm. of 0·5 per cent. solution of procaine without adrenaline is slowly injected. Before the injection the piston is pulled a little back, so that one is sure of not injecting into the carotid artery. (I always have evipan on hand in case the parathyroid gland should be affected.) The patient is warned not to make any swallowing movement while the needle is introduced and during

the injection. Steinbrocker calls the injection a stellate block, which in most cases it is, but even if the needle comes into contact with the sympathetic above the ganglion the same result is achieved, because part of the liquid presses down on the ganglion.

To some of the patients the injection is so disagreeable, on account of the region in which the injection takes place, and also because they are not permitted to do any swallowing, that one has to stop before the intended quantity has been injected. In other cases there has been such a pronounced relief from pain and stiffness that the patient himself has expressed the desire to continue.

Results

Since last year I have treated about fifty patients with this form of sympathetic block. I have analysed the results in the first twenty-four patients. The shoulder-hand syndrome was the main indication for operation, and these patients made up sixteen of the twenty-four. The remaining eight were patients without this symptom but with, for example, pains in the shoulder and arm only, but of such violence that I found it worth while to try the block with the sole object of relieving the pain. I have also treated two patients with helodermi (fibrous pads on the dorsal aspect of the middle joints of the fingers), and a few others. Altogether these twenty-four patients have had eighty-six blocks (see Table).

Most patients had consulted me privately, with the result that routine tests, especially measuring of the skin temperature and the perspiration test, were not undertaken. The selection of patients and assessment of the result of injection was purely clinical. Unless otherwise stated, the ordinary medical and neurological examination showed nothing abnormal.

Some of the patients were women at the climacteric and with climacteric characteristics; that is to say, they were as a whole rather fat and with puffy subcutaneous tissues. All the patients have formerly been given physical treatment with no satisfactory result.

Horner's symptom presented itself after approximately 40 per cent. of the injections, but the result seemed independent of the occurrence of Horner's symptom. As can be seen from the Table, in the group with periarthrosis humero-scapularis about 60 per cent. of the cases improved and there was no effect in 40 per cent. In no case did the block aggravate the condition or produce lasting discomfort.

The improvement has mostly been in diminution of pain and also of swelling and stiffness of the fingers and hands. The relief has often come immediately after the injection. In one patient the effect was excellent: after an attack of reflex dystrophy four years before, two fibrous nodules appeared in the first interstitials, and fibrous tension in the thenar, analogous to Dupuytren's contraction. The nodules were much softer after two injections; one of them disappeared completely, and the hand became more supple and soft. In the case of a patient with helodermi the nodules became softer after the first injection; she was able to put on her rings, which she had been unable to do for five or six years, but the good effect disappeared during the following two months, and no improvement followed a series of injections a few months later. In another patient with helodermi the operation was without result.

The cause of the result of the treatment is

TABLE

ANALYSIS OF RESULTS OF STELLATE GANGLION BLOCK

	Number		Average age		Duration (average number of months)		Average number of injections		Effect	
									Unchanged	Improved
	M.	F.	M.	F.	M.	F.	M.	F.		
Periarthrosis humeri with secondary dystrophy ..	4	12	55	34	4	6*	4	4	6	10
Other cases	4	4	47	42	½ to many years	One month many years	2	3	6	2

* Excluding a single case of four years' duration.

uncertain : various explanations exist. As the ailment is supposed to be due to a dysfunction of the sympathetic one can assume that the effect of the block depends on a paralysis of the sympathetic, which is part of the reflex curve that keeps the disturbance of circulation going. The soothing effect may be due to the fact that the pain is purely " sympathetic " (Shaw, 1933). Mason (1948) refers to a case of shoulder-hand syndrome treated with the same technique.

Conclusions

After the injection in the stellate ganglion with 10 c.cm. of 0·5 per cent. procaine solution, improvement was obtained in 60 per cent. of patients with periarthrosis humeroscapularis with secondary reflex dystrophic disturbances of the hand ; 40 per cent. remained unchanged. The injection technique is difficult and the injection is a little disagreeable for most patients, but hardly dangerous.

In acute cases there may be improvement of pains and swelling of fingers and hand, and in chronic cases improvement in the stiffness of hand and fingers may take place, and fibrous nodules may disappear.

It is true that this series is small and, as the symptoms of the disease were not clearly defined, the indications for the treatment rested on a rather vague clinical judgment, the patients not having been submitted to laboratory investigations and no perspiration test or skin-temperature measurements having been done. Nevertheless, I have reported the results because periarthrosis humeroscapularis with secondary reflex dystrophy is a long drawn out and painful ailment, and if the hand is also included one is even less certain about the duration and prognosis. I consider therefore that any sensible therapeutic measure should be taken to shorten or relieve the disease.

References

Gillmor, C. (Personal communication.)
Kahlmeter, G. (1936). *Nord. med. Tidsskr.*, **12**, 1435.
Mason, R. M. (1948). *Annals of the Rheumatic Diseases*, **7**, 30.
Shaw, R. C. (1933). *Arch. Surg.*, **27**, 1072.
Steinbrocker, O. (1947). *Annals of the Rheumatic Diseases*, **6**, 80.

Bloc Sympathique Cervical dans la Périarthrose de l'Articulation de l'Epaule avec Dystrophie Secondaire Réflexe

Une injection de 10 mm.c. de solution de procaïne à 0·5 pour cent dans le ganglion étoilé fut suivie d'une amélioration dans 60 pour cent des cas de périarthrose huméro-scapulaire avec des troubles dystrophiques réflexes sécondaires de la main ; 40 pour cent demeurèrent inchangés. La technique de l'injection est difficile et l'injection est un peu désagréable pour la plupart des malades, mais elle n'est guère dangereuse.

Dans des cas aigus il peut y avoir une amélioration des douleurs et de l'enflement des doigts et de la main, et dans des cas chroniques une amélioration de la rigidité de la main et des doigts peut se produire ; les nodules fibreux peuvent disparaître.

Il est vrai que cette série est petite et, comme les symptômes de la maladie n'étaient pas clairement définis, les indications du traitement se basaient sur un jugement clinique plutot vague ; les malades ne furent pas soumis à l'examen de laboratoire, l'épreuve sudorale ne fut pas faite et la température de la peau ne fut pas déterminée. Malgré cela j'ai rapporté sur ces résultats parce que la périarthrose huméro-scapulaire avec dystrophie réflexe secondaire est una maladie pertinace et douloureuse, et lorsque la main se trouve également atteinte, on est encore moins certain de la durée et du pronostic. Je pense donc que n'importe quelle mesure thérapeutique judicieuse doit être prise afin d'abréger la maladie ou de soulager le malade.

ESTIMATION OF GOLD IN BIOLOGICAL FLUIDS

BY

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Chrysotherapy has now become a recognized form of treatment in rheumatoid arthritis and much experimental work has been done to determine the fate of gold salts in the body. Kling and his colleagues (1939) showed that gold compounds were deposited mainly in reticulo-endothelial cells, of which synovial membrane contains a large number. They were able to detect spectrographically the presence of gold in synovial fluids, even after the administration of such a small amount of gold salt as 350 mg. According to Rosenberg (1942), gold enters almost every cell in the body shortly after injection, the greatest concentration being found in the liver, spleen, kidneys, and skin.

Block and Buchanan (1940) claimed to have devised an accurate and specific microcolorimetric method for the determination of small amounts of gold in biological fluids such as blood and urine. This method has been used extensively by these workers and their colleagues to study the metabolism of injected gold salts (Block, Buchanan, and Freyberg, 1941, 1942 ; Freyberg, Block, and Levey, 1941, 1942 ; Freyberg, 1942 ; Freyberg, Block, and Wells, 1942 ; Block, 1944). They found that, when intramuscular injections of myochrysine were given at weekly intervals and when the dosage was kept at a constant level (100 mg. myochrysine, that is, 50 mg. gold) the concentration of plasma gold remained fairly constant (0·4 to 0·8 mg. per 100 ml.). Furthermore, during the period of administration much of the gold was retained in the body. With a weekly injection of 50 mg. of gold, the average daily excretion, mainly in the urine, was 1 mg. Thus during treatment about 80 per cent. of the injected gold remained in the body. After a course of injections gold could be recovered from the blood and urine for long periods, even up to one year.

During an investigation into the effect of BAL (2 : 3-dimercaptopropanol) on patients receiving myochrysine for rheumatoid arthritis, we decided to use the method of Block and Buchanan (1940) to estimate the amount of gold in blood and urine before and during BAL administration. Their technique was carried out in the strictest detail.

Method

The method devised by Block and Buchanan (1940), a modification of the technique described by Pollard (1937), depends on the use of a colour reaction produced by o-dianisidine and gold chloride in a slightly acid buffered solution, the colour being measured quantitatively in a photo-electric colorimeter. Preliminary digestion of the blood and urine with sulphuric acid and hydrogen peroxide is followed by conversion of the separated gold into gold chloride by the addition of aqua regia.

TABLE 1

DAILY RESULTS IN A PATIENT RECEIVING 100 mg. MYOCHRYSINE AT WEEKLY INTERVALS

Day	Myochrysine (mg.)	Plasma gold mg./100 c.cm.	Urinary gold mg./24 hrs.
1	100	—	—
2	—	Nil	0·66
3	—	Nil	0·58
4	—	0·10	0·80
5	—	0·18	1·31
6	—	Nil	0·39
7	—	0·20	0·61
8	—	0·20	2·68
9	100	0·15	2·57
10	—	Nil	0·50
11	—	0·12	1·39
12	—	Nil	0·84
13	—	0·23	1·15
14	—	Nil	0·29
15	—	Nil	Nil

Results

Over 150 samples of blood and urine were taken from a series of patients with rheumatoid arthritis who were receiving injections of myochrysine, and examined quantitatively for gold content. In some instances the estimations were done daily and in others at weekly intervals. At first single observations were performed on each specimen, but it soon became apparent that the results showed great variation, even when the weekly dosage of myochrysine was kept constant. A typical example is shown in Table 1.

It was therefore decided to control the method by estimating each specimen in duplicate or triplicate. This was done on a large number of samples of blood and urine, and we found that in most instances the results were not comparable. Table 2 shows the figures obtained in eight cases.

TABLE 2

RESULTS OF TRIPLICATE ANALYSIS OF SINGLE SPECIMENS OF BLOOD AND URINE FROM EIGHT PATIENTS ON CHRYSOTHERAPY

Case	Plasma gold mg./100 c.cm.	Case	Urinary gold mg./24 hrs.
1	Nil 0·22 0·50	5	0·92 2·54 2·11
2	0·23 Nil 0·47	6	0·74 1·80 4·05
3	Nil 0·30 Nil	7	2·98 4·40 0·92
4	0·47 0·22 0·10	8	1·31 Nil 0·80

Ampoules from the batch of myochrysine used during the investigation were analysed by the same method; the expected result was obtained on only one occasion. The estimation of known amounts of gold chloride added to both plasma and urine also gave disappointing results (Table 3). On the other hand we found, as originally described by Pollard (1937), that gold could be recovered with a considerable degree of accuracy when measured amounts of gold chloride were added to simple aqueous solution (Table 4).

TABLE 3

RECOVERY OF KNOWN AMOUNTS OF GOLD ADDED TO PLASMA AND URINE

Plasma		Urine	
Gold added μg.	Gold recovered μg.	Gold added μg.	Gold recovered μg.
20	Nil	50	Nil
20	18·6	50	14·3
20	15·0	50	23·2
20	Nil	50	Nil
20	5·5	50	15·4

TABLE 4

RECOVERY OF KNOWN AMOUNTS OF GOLD CHLORIDE (CALCULATED AS GOLD) ADDED TO SIMPLE AQUEOUS SOLUTION

Gold added μg.	Gold recovered μg.
5	4·5
10	10·8
20	19·2
40	40·2

Discussion

Our object in presenting this paper is to demonstrate that, in our hands, the method of Block and Buchanan (1940) for estimating gold levels in plasma and urine has yielded inaccurate results. Pollard's technique, which applies only to recovery of gold from simple aqueous solution, is eminently satisfactory, but we think that in its application to biological fluids it is far from reliable.

Macleod (1948) investigated the effect of BAL on urinary gold excretion by this method and found that the results, in the three cases studied, were very unsatisfactory as judged by estimation of duplicate samples.

Previous literature on the subject makes no mention of the anticoagulant used in the plasma estimations. Potassium oxalate was our original choice, and it was thought that this might be responsible for the erratic results of the blood levels because of the possible interaction of oxalate and gold chloride (Tukats, 1933). The substitution of heparin, however, produced no improvement.

As yet there does not appear to be an accurate method of determining the amount of gold in biological fluids and the published views on the rate of absorption of gold from the site of injection and on its elimination from the body should, therefore, be accepted with reserve. Further research on this aspect of gold therapy is both necessary and desirable.

Summary

1. Previous work on the estimation of gold in plasma and urine is briefly reviewed.

2. An investigation of the blood and urinary gold levels, by the method of Block and Buchanan (1940), in a series of patients with rheumatoid arthritis who were receiving chrysotherapy is described. Unreliable results were obtained as judged by the estimation of duplicate and triplicate samples.

3. The opinion is expressed that there is not as yet an accurate method for estimating gold in biological fluids.

REFERENCES

Block, W. D. (1944). *Annals of the Rheumatic Diseases*, **4**, 39.
——, and Buchanan, O. H. (1940). *J. biol. Chem.*, **136**, 379.
——, ——, and Freyberg, R. H. (1941). *J. Pharmacol.*, **73**, 200.
——, ——, —— (1942). *Ibid.*, **76**, 355.
Freyberg, R. H. (1942). *Proc. Mayo Clin.*, **17**, 534.
——, Block, W. D., and Levey, S. (1941). *J. clin. Invest.*, **20**, 401.
——, ——, —— (1942). *Annals of the Rheumatic Diseases*, **3**, 77.
——, ——, and Wells, G. S. (1942). *Clinics*, **1**, 537.
Kling, D. H., Sashin, D., and Spanbock, J. (1939). *J. Lab. clin. Med.*, **24**, 1241.
Macleod, J. G. (1948). *Annals of the Rheumatic Diseases*, **7**, 143.
Pollard, W. B. (1937). *Analyst*, **62**, 597.
Rosenberg, E. F. (1942). *Proc. Mayo Clin.*, **17**, 264.
Tukats, S. (1933). *Biochem. Z.*, **260**, 143.

Détermination de l'Or dans les Liquides Biologiques

RÉSUMÉ

On revise brèvement les travaux précédents sur la détermination de l'or dans le plasma et dans l'urine. On décrit l'investigation du niveau de l'or dans le sang et dans l'urine par la méthode de Block et Buchanan (1940) dans une série de malades atteints d'arthrite rhumatismale et soumis à la chrysothérapie. Des résultats inconstants furent obtenus, jugeant d'après la détermination de deux ou trois échantillons similaires. On exprime l'opinion qu'une méthode exacte pour déterminer l'or dans les liquides biologiques n'existe pas encore.

SALAZOPYRIN IN THE TREATMENT OF RHEUMATOID ARTHRITIS

BY

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and

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In several reports (1941a, b, 1942, 1944, 1948) published during recent years Professor Nanna Svartz has claimed good results in the treatment of rheumatic polyarthritis from the use of a sulphapyridine compound. The drug, which has been given the name salazopyrin, is obtained by the chemical combination of salicylic acid and sulphapyridine and has the formula 4-/pyridyl (2) amido sulphonyl/-3′-Carbody-4′-oxyazobenzene.

It is claimed that the drug has a specific affinity for connective tissue, where subsequent disintegration gives rise to amino-salicylic acid and sulphapyridine. Svartz (1948) believes that the essential lesion in rheumatic disease is located in connective tissue and is inflammatory in nature. On this basis she argues that drugs with an affinity for connective tissue are most likely to be of value in treatment. The value of salicylates in ameliorating the symptoms of rheumatic fever is accepted. Unless organisms are present in the inflamed connective tissue, the desirability of attaining a high local concentration of sulphapyridine is more in doubt. Few observers believe that there is such a dissemination of bacteria in rheumatic fever or in rheumatoid arthritis.

The initial dosage recommended by Svartz was 6 g. in twenty-four hours. This was reduced to 1 to 1½ g. daily as the condition improved. In chronic rheumatoid arthritis she advocates the use of the drug over a long period. Some of her patients have consumed 5,000 to 6,000 ½-g. tablets in one to two years. Toxic effects are said to be relatively rare, the commonest being fever, skin rashes, nausea, and vomiting. These symptoms subside quickly when the drug is withdrawn.

Svartz divided her cases into acute and chronic rheumatic polyarthritis, and claimed that benefit was obtained in both instances. This classification makes it difficult to assess her results. For the chronic group she also uses the term "chronic rheumatoid arthritis" so the effects of the drug in this group will be considered in more detail.

KEY TO CHART

JOINTS INVOLVED :

1. Joint not involved.
2. Pain, swelling, limitation of movement : *active stage.*
3. Residual damage, but no active inflammation : *inactive stage.*
4. Moderate activity, intermediate between 2 and 3.

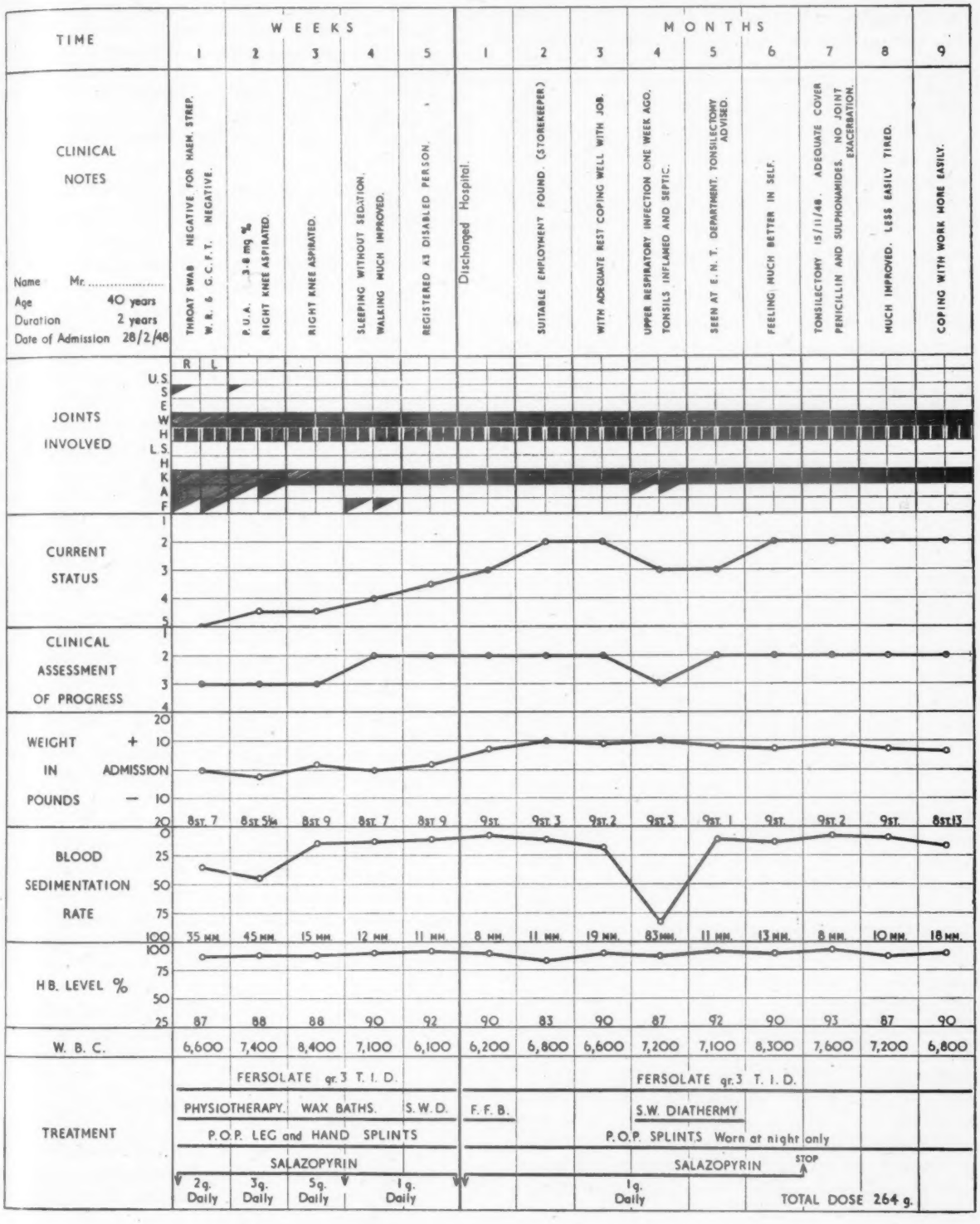
U.S. = upper spine.	L.S. = lower spine.
S. = shoulders.	H. = hips.
E. = elbows.	K. = knees.
W. = wrists.	A. = ankles.
H. = hands and fingers.	F. = feet.

CURRENT STATUS :

1. Return to full normal occupation.
2. Return to modified occupation or selected employment.
   (a) Working and attending for out-patient treatment.
3. Not working, attending for out-patient treatment.
   (a) In-patient—attending physiotherapy department, and allowed out of hospital.
4. Ambulatory in the ward.
   (a) Confined to bed, but allowed up to bathroom.
5. Completely confined to bed.

CLINICAL ASSESSMENT :

1. *Joints :* movement good, power good, no pain.
   Health : satisfactory—eating and sleeping well.
2. *Joints :* moderate limitation of movement, some pain, power fair.
   Health : good, but easily tired.
3. *Joints :* marked limitation of movement, pain, swelling, power poor.
   Health : fair, capacity for exercise strictly limited.
4. *Joints :* very little movement, pain, swelling, marked loss of power.
   Health : poor, fatigue, anorexia, fever, loss of weight.


TIME
WEEKS 1 2 3 4 5
MONTHS 1 2 3 4 5 6 7 8 9
CLINICAL NOTES
Name Mr.
Age 40 years
Duration 2 years
Date of Admission 28/2/48
THROAT SWAB NEGATIVE FOR HAEM. STREP.
W. R. & G.C.F.T. NEGATIVE.
P.U.A. 3-8 mg %
RIGHT KNEE ASPIRATED.
RIGHT KNEE ASPIRATED.
SLEEPING WITHOUT SEDATION.
WALKING MUCH IMPROVED.
REGISTERED AS DISABLED PERSON.
Discharged Hospital.
SUITABLE EMPLOYMENT FOUND. (STOREKEEPER)
WITH ADEQUATE REST COPING WELL WITH JOB.
UPPER RESPIRATORY INFECTION ONE WEEK AGO. TONSILS INFLAMED AND SEPTIC.
SEEN AT E. N. T. DEPARTMENT. TONSILECTOMY ADVISED.
FEELING MUCH BETTER IN SELF.
TONSILECTOMY 15/11/48. ADEQUATE COVER PENICILLIN AND SULPHONAMIDES. NO JOINT EXACERBATION.
MUCH IMPROVED. LESS EASILY TIRED.
COPING WITH WORK MORE EASILY.
JOINTS INVOLVED
R L
U.S.
S
E
W
H
L.S.
H
K
A
F
CURRENT STATUS
CLINICAL ASSESSMENT OF PROGRESS
WEIGHT IN POUNDS + ADMISSION −
8st. 7 8st 5½ 8st 9 8st. 7 8st 9 9st. 9st. 3 9st. 2 9st. 3 9st. 1 9st. 9st. 2 9st. 8st.13
BLOOD SEDIMENTATION RATE
35 MM. 45 MM. 15 MM. 12 MM. 11 MM. 8 MM. 11 MM. 19 MM. 83MM. 11 MM. 13 MM. 8 MM. 10 MM. 18 MM.
HB. LEVEL %
87 88 88 90 92 90 83 90 87 92 90 93 87 90
W. B. C.
6,600 7,400 8,400 7,100 6,100 6,200 6,800 6,600 7,200 7,100 8,300 7,600 7,200 6,800
TREATMENT
FERSOLATE gr. 3 T. I. D.
PHYSIOTHERAPY. WAX BATHS. S.W.D.
P.O.P. LEG and HAND SPLINTS
SALAZOPYRIN
2g. Daily
3g. Daily
5g. Daily
1g. Daily
F. F. B.
FERSOLATE gr. 3 T. I. D.
S.W. DIATHERMY
P.O.P. SPLINTS Worn at night only
SALAZOPYRIN
STOP
1g. Daily
TOTAL DOSE 264 g.

During the years 1941-45, 475 cases of the chronic type were given salazopyrin. The minimum period of follow-up was two years. Patients were sent a questionnaire and 307 replies were received. One hundred and ninety-four patients (63 per cent.) had recovered or showed improvement. In eighty-nine (29 per cent.) the condition was unchanged or had deteriorated. Twenty-four had died. The questionnaire revealed that many patients had failed to continue with treatment after discharge from hospital, but of the 16 per cent. who continued to take the drug for a lengthy period, three-quarters were cured or substantially improved.

Fletcher (1944) reported on the use of salazopyrin in five cases of rheumatic fever, one of gonococcal arthritis, two of acute infective arthritis, and six of chronic infective arthritis. In this last group only one patient was treated for as long as six months and the total dose was 180 g. This patient and one other, treated for three months, stated that they felt better, but there was little clinical evidence of improvement and the blood sedimentation rate did not return to normal.

The Present Investigation

In view of the substantial claims made by Svartz as to the value of salazopyrin in chronic rheumatoid arthritis it was decided to submit the drug to further clinical trial. A supply of salazopyrin was obtained from Sweden through the courtesy of Professor Svartz, and twenty cases of rheumatoid arthritis were treated. In view of the difficulty in assessing the value of any form of therapy in a chronic disease without adequate controls, the results in these cases were compared with those obtained in a group receiving gold, and in a third group receiving no specific therapy. All sixty cases were treated initially as in-patients and all were subjected to the same basic regime of treatment in the rheumatic unit. This included rest in bed, dietary supplements, rest splints, physiotherapy, and remedial exercises. It is recognized that this regime alone will lead to substantial improvement in the majority of cases of rheumatoid arthritis, but it was felt that when the results in the three groups were finally compared in detail, some indication would be obtained as to whether salazopyrin had any specific effect on the disease. The inclusion of a group receiving gold therapy was considered desirable, as it allowed comparison with patients receiving a drug believed to be of real value in this disease.

The clinical details and laboratory investigations in each patient were entered on a chart specially designed for the purpose (see Figure). The patients were examined and assessed on each occasion by the same observer (R.J.G.S.). The key to the chart is given in full. It was felt that the routine charting of all relevant data at intervals both during in-patient treatment and during the follow-up period by one observer would enable the final assessment of patients in each of the three groups to be made with a reasonable degree of accuracy. The method will be modified and improved in the light of further experience.

The dose of salazopyrin used was initially that recommended by Svartz—6 g. in twenty-four hours. Twelve of the first fourteen patients receiving this amount showed toxic reactions within four to five days, varying from slight headache and nausea to high fever and rashes. Some showed red blood cells in the urine. The symptoms subsided immediately the drug was stopped. Five patients were given anthisan up to 800 mg. daily for several days, then full doses of salazopyrin were resumed. Toxic reactions again developed in each of these cases. In subsequent cases the initial dose was reduced to 2 g. daily and increased gradually to 5 g. daily. On this regime toxic reactions were mild and infrequent. Patients were discharged from hospital on a maintenance dose of 1 g. daily. Table 1 gives details of these patients. During their stay in hospital the data shown in the chart was noted at weekly intervals. After discharge patients reported to the follow-up clinic once a month. The same procedure was followed for the cases on gold and for those receiving no specific therapy. The group on gold all received a standard course, starting with four injections of 0·01 g. myochrysin at weekly intervals. The dose was then raised to 0·05 g. weekly and maintained at that level till 1 g. had been given. Injections had to be stopped in three cases because of mild toxic reactions.

All patients on discharge from hospital claimed to be substantially improved. A few of those on salazopyrin believed that they had definitely benefited from taking the drug. An analysis of the results (Table 2) shows that in sixteen cases on salazopyrin the clinical assessment on discharge from hospital had improved ; fourteen had moved up from grades 4 and 3 to grade 2, and two had reached grade 1. On the final assessment, however, five had dropped back to grade 3.

Improvement was slightly better maintained in those receiving gold, eighteen remaining in the two upper grades on final assessment. The results in the controls are almost identical with those on salazopyrin. Table 3 shows the haemoglobin levels in the three groups. The results are again slightly in favour of those patients receiving gold.

Analysis of blood sedimentation rates (Table 4) shows no significant differences between the three

TABLE 1

SALAZOPYRIN : DOSAGE AND LENGTH OF COURSE

No.	Sex	Age	Duration of symptoms in years	Total dose (g.)	Toxic reactions	Length of course (days)	Stay in hospital (weeks)	Follow-up (months)
1	M.	48	0·5	33	Rash, fever	14	15	11
2	M.	24	19	60	Rash, nausea	26	12	6
3	F.	39	8	88	Depression	30	11	10
4	F.	43	2	240	—	180	6	10
5	M.	60	20	340	—	135	21	6
6	F.	43	10	35	Rash, nausea	15	5	9
7	M.	41	1·5	253	—	98	18	6
8	F.	36	1·25	74	Rash, nausea	69	4	9
9	F.	41	8	51	Nausea	40	5	9
10	F.	46	0·5	80	—	30	10	7
11	M.	46	2	181	—	97	11	3
12	F.	38	21	203	—	74	11	7
13	M.	35	7	86	—	60	14	5
14	F.	57	3	105	—	52	8	6
15	M.	35	1·5	126	—	49	9	6
16	M.	40	0·16	135	—	63	6	6
17	M.	51	0·33	112	—	58	5	5
18	F.	50	1·5	85	—	42	4	5
19	M.	23	3	116	—	35	9	3
20	F.	55	5	50	—	30	21	2

TABLE 2

ANALYSIS OF RESULTS

	Sex		Average (years)	Average duration of symptoms (years)	Average no. of weeks in hospital	Average follow-up (months)	Clinical Assessment*												No. of patients who relapsed
							Admission to hospital				Discharge from hospital				Final follow-up				
	M.	F.					4	3	2	1	4	3	2	1	4	3	2	1	
Salazopyrin ..	10	10	42·6	5·7	10·2	6·5	4	10	6	—	—	—	18	2	—	5	12	3	11
Gold	5	15	41·2	4·7	6·5	8·0	1	6	12	1	—	1	16	3	—	2	12	6	8
Controls	5	15	47·1	7·0	5·8	6·2	2	10	8	—	—	1	13	6	—	5	11	4	8

* See key to chart for assessment of grades

TABLE 3

HAEMOGLOBIN ESTIMATION

	Admission to hospital			Discharge from hospital			Final follow-up		
	60-70%	71-80%	81-100%	60-70%	71-80%	81-100%	60-70%	71-80%	81-100%
Salazopyrin ..	3	1	16	—	2	18	—	3	17
Gold	—	4	16	—	2	18	—	1	19
Controls	—	3	17	—	—	20	—	3	17

TABLE 4

B.S.R. ESTIMATION

	Admission to hospital			Discharge from hospital			Final follow-up		
	Normal 0-10	Moderately raised 11-40	Markedly raised 41-100	Normal 0-10	Moderately raised 11-40	Markedly raised 41-100	Normal 0-10	Moderately raised 11-40	Markedly raised 41-100
Salazopyrin ..	1	13	6	4	8	8	5	10	5
Gold	2	11	7	—	12	8	5	12	3
Controls	3	10	7	6	12	2	5	10	5

groups. The B.S.R. remained raised in fifteen cases in each. Table 5 shows the proportions of patients who gained or lost weight during their stay in hospital and during the follow-up period. The results again favour the patients on gold.

TABLE 5

FLUCTUATION IN WEIGHT

	In hospital			Final follow-up		
	Gain (over 2 lb.)	Static (less than 2 lb. gain or loss)	Loss (over 2 lb.)	Gain (over 2 lb.)	Static (less than 2 lb. gain or loss)	Loss (over 2 lb.)
Salazopyrin	12	3	5	6	5	9
Gold ..	8	6	6	5	8	7
Controls ..	6	10	4	8	1	11

Discussion

In the final analysis of results in the three groups of patients, those receiving gold, in addition to the basic regime of treatment, appeared to benefit the most. There is no appreciable difference between the group receiving salazopyrin and those given no specific therapy, in spite of the fact that the patients receiving salazopyrin were retained in hospital longer for the purposes of the experiment. The scope of the clinical trial was limited but it is felt that, had salazopyrin been of any real value in modifying the course of the disease, some indication of its action in this respect would have been obtained. It might be objected that the total dose and length of course were not those recommended in the original reports, but the incidence of toxic reactions was unduly high when large initial doses were given. With regard to the length of course, it is generally admitted that if any single method of therapy is continued for long enough in rheumatoid arthritis, it is likely that a natural remission of the disease will occur, and credit may be wrongly given to that particular remedy.

The theoretical basis for the use of salazopyrin in rheumatoid arthritis—that it has a specific affinity for connective tissue where it disintegrates into sulphapyridin and aminosalicylic acid—cannot be regarded as sound. Salicylates have no specific effect in this disease, nor has any member of the sulpha group of drugs. Penicillin and streptomycin have been equally ineffective. This is not surprising as few observers now believe that living organisms play a direct part in the production of the changes in connective tissue.

Summary

1. The drug salazopyrin has been used in the treatment of twenty cases of rheumatoid arthritis.

2. The results obtained have been compared with those in twenty cases treated with gold and twenty cases in whom no specific therapy was given.

3. All three groups were studied as in-patients and followed up for six to eight months.

4. All three groups underwent the same basic regime of treatment.

5. The method of case-recording is described.

6. Salazopyrin does not appear to be of any specific value in the treatment of this disease.

The authors wish to express their gratitude for the help given by the medical and nursing staff of the Rheumatic Unit, Northern General Hospital, Edinburgh.

References

Fletcher, E. (1944). *Med. World*, **60**, 697.
Svartz, N., and Kallner, S. (1940). *Nord. Med.*, **8**, 1935.
—— (1941a). *Nord. M d.*, **9**, 554.
—— (1941b). *Ibid.*, **11**, 2261.
—— (1942). *Acta med. scand.*, **110**, 577.
—— (1944). *Nord. Med.*, **23**, 1713.
—— (1948). *Ibid.*, **37**, 299.
—— (1948). *Rheumatism*, **4**, 180.
——, Kallner, S., and Helander, S. (1945). *Nord. Med.*, **25**, 211.

Salazopyrine dans le Traitement de l'Arthrite Rhumatismale

Résumé

Le médicament salazopyrine fut employé dans le traitement de vingt cas d'arthrite rhumatismale. Les résultats furent comparés avec ceux obtenus dans vingt cas soumis à la chrysothérapie et dans vingt cas sans aucun traitement spécifique. Les malades des trois groupes étudiés se trouvaient hospitalisés et ils furent surveillés pendant six à huit mois. Les trois groupes furent soumis au même régime fondamental de traitement. On décrit la méthode suivie pour compiler le dossier clinique des malades.

La salazopyrine ne semble avoir aucune valeur spécifique dans le traitement de cette maladie.

THE VALUE OF REPEATED COLLOIDAL GOLD TESTS IN RHEUMATOID ARTHRITIS

BY

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It has been shown by several workers that the colloidal gold test is positive in a proportion of cases of rheumatoid arthritis ; in 76 per cent. of a series of twenty-four by Carter and Maclagan (1946), in 71 per cent. of a series of eleven by Rennie and Rae (1947), and in 61 per cent. of a series of a hundred by Fraser (1948). Although the latter performed 133 tests in the hundred cases, none of these workers made repeated observations on the same cases over a period to see whether the test altered with the passage of time or with changes in clinical condition. This present investigation was undertaken in order (*a*) to confirm the observation that the gold sol reaction was indeed positive in a proportion of cases of rheumatoid arthritis ; (*b*) to see whether the test varied over a period of time or with a change in the clinical condition ; and (*c*) to try to discover the significance of the test in the light of clinical and other observations.

Material and Technique

The patients in this series of cases all suffered from rheumatoid arthritis according to the accepted diagnostic criteria for that disease ; sixty-five were in-patients, and five were out-patients of the Rheumatic Unit of the Northern General Hospital, Edinburgh, and two were from the general wards of the same hospital.

Serum for the test was obtained by centrifuging a specimen of venous blood which had been allowed to clot and then stored overnight in a refrigerator. The test was performed at weekly, fortnightly, or monthly intervals, depending whether the patient was in the wards or attending the follow-up clinic. The method of performing the test and the gold sol used were those recommended by Maclagan (1944). The reaction was allowed to stand for twenty-four hours at room temperature and the result then interpreted as follows : no precipitation as negative ; slight precipitation, just visible on shaking as 1 ; slight colour loss as 2 ; more colour loss as 3 ; supernatant fluid just coloured as 4 ; and complete precipitation as 5.

The blood sedimentation rate was estimated on every occasion that a gold test was performed using Westergren's technique (1926), and the fall at the end of one hour was recorded.

TABLE I

NUMBER OF TESTS DONE

Number of tests	Number of months between first and last test										
	1	2	3	4	5	6	7	8	9	10	11
1											
2	5	4		1	3						
3	3	1	4		1	1			1		
4	2	6	5	1	3	1					
5		1	2	2		1					
6			4		1		1				
7					1	2		1	1		
8											
9					1						1
10											
11				1		1					

The table shows the number of tests, the numbers of patients on whom they were performed, and the interval between the first and last test. The eight patients on whom only a single test was performed are omitted.

Results

The results in 72 cases are available for analysis. The number of observations and the period over which they were made are shown in Table 1. The age incidence is given in Table 2, and shows that the series is in keeping with the expected age incidence of the disease (Sclater, 1943).

Of the seventy-two cases in the series, thirty-five (49 per cent.) had always a negative test, and thirty-seven (51 per cent.) had one or more positive tests. This confirms the previous observations that the test is positive in a proportion of cases of rheumatoid arthritis. In eight cases, on which the test was only performed once, it was positive in five and negative in three. Of the remaining sixty-four

tested on more than one occasion, forty-three (50 per cent.) were always negative, eight (12·5 per cent.) were always positive, and twenty-four (37·5 per cent.) were sometimes positive and sometimes negative. The thirty-two patients who were consistently negative were tested, on an average, three times ; the twenty-four in whom both positive and negative results were obtained were tested, on an average, six times. It is likely, therefore, that a proportion of the patients in the first group would have passed into the second if tested more often and over a longer period.

In the whole series there were forty-eight women and twenty-four men, an incidence of 2 : 1. The analysis of the sixty-four cases in which the test was carried out more than once is presented in Table 3. It will be seen that there is no difference between the sexes in the results obtained.

The results were also examined critically to see whether they bore any relation to clinical activity, progress and prognosis, duration of the disease, tissue damage, gold therapy, and muscle biopsy findings.

TABLE 2

AGE INCIDENCE

Sex	Age groups							
	5-14	15-24	25-34	35-44	45-54	55-64	65-74	over 75
Females		1	4	14	12	8	6	1
Males		2	2	10	7	3	1	

Female mean age = 48·8 years.
Male mean age = 42·7 years.

TABLE 3

SEX INCIDENCE

Sex	Positive tests		Negative tests		Varying tests	
	Cases	%	Cases	%	Cases	%
Female	5	12	23	53	15	35
Male	3	14	10	48	8	38

The single tests performed in eight cases are omitted.

Clinical Activity.—The cases were divided into two groups ; active and inactive, according to the following criteria : the blood sedimentation rate, the state of the joints, and constitutional signs such as changes in weight and the presence or absence of fever and fatigue.

Sixty-two cases were considered to be active and ten to be inactive cases. Of the former, twenty-eight always had a negative test, and thirty-two had at least one positive test ; of the latter, inactive cases, seven were always negative, and three had at least one positive test. Thus, although the number of results amongst the inactive cases was too small from which to draw conclusions, there were almost equal numbers of negative and positive results amongst the active cases, so that it can be concluded that a single test is of no value in deciding whether the case is active or not.

Progress and Prognosis.—Repeated tests appear to help in giving a prognosis. In Table 4 it can be seen that of the thirty-two cases observed more than once who gave at least one positive result fifteen went on to give negative reactions and improved clinically ; eleven others, however, in spite of clinical improvement, continued to give positive reactions, although in seven of them there

TABLE 4

CLINICAL PROGRESS IN CASES WITH AT LEAST ONE POSITIVE TEST

Cases showing clinical improvement				Cases showing progressive deterioration	
Case No.	Final gold test negative	Case No.	Final gold test positive	Case No.	Results of tests
1	4 0 0	16	4 4 3 3	27	1 1 5 5
2	4 1 1 0 0	17	0 5 4 3	28	0 3 4 5 3 3 2 0 5 5 5
3	4 4 4 3 2 1 0	18	1 3 4 0 3 0 1	29	1 5
4	5 3 4 1 0 0 0	19	4 1 1 3	30	2 4 4
5	0 0 1 2 0 0 0 0 0 0 0	20	1 4 1 0 1 2	31	4 4 0 4 2 0 5 0 5
6	3 0 0 1 0 0	21	1 1 1	32	0 1 5
7	1 1 0 1 0 0 0	22	1 0 2		
8	1 0 0	23	0 0 1		
9	1 0 0 0 0	24	1 1		
10	1 1 1 0	25	0 0 1 2		
11	0 3 0	26	4 5 4 4 5		
12	0 2 3 3 0 0				
13	1 0 1 0				
14	3 0				
15	0 1 0 0 1 0				

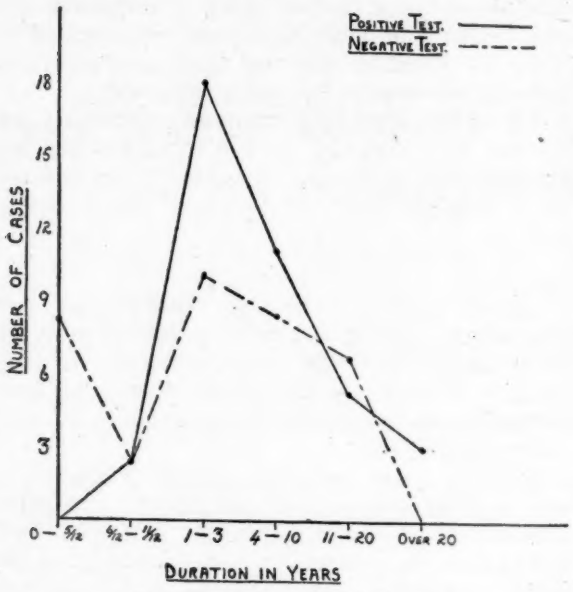

FIGURE.—Duration of disease.

was a tendency for the results of the test to be less strongly positive. Six cases that had very strongly positive tests, (all except one had a 5), remained clinically very active ; these six were the most seriously ill of the whole series, one dying (Case 32) and another (Case 31) becoming moribund after being discharged home at her own request ; four (Cases 27 to 30) ran into an active phase of the disease, Case 28, in particular, being severely affected.

There was one exception to this, Case 26 ; this man was not seriously affected, although his test results were consistently very strongly positive, and he made a good clinical recovery. It was thought, therefore, that some other cause might be responsible but full clinical investigation failed to reveal it. In this connexion, it may be mentioned that two other cases both had strongly positive results but were not suffering from severe arthritis. In one, the disease was of only six weeks' duration, and he had had syphilis and gonorrhoea less than twelve months previously ; in the other, the duration was of several years, but he had a positive Wassermann reaction and was undergoing anti-syphilitic treatment while in the rheumatic unit. It is likely that these specific conditions were responsible for the positive results, and as the issue was confused they were omitted from the series.

It would appear, therefore, that in the absence of other pathological conditions, repeated strongly positive results, especially including some 5's, are of grave significance. It should be noted that undue gravity need not be attached to a single 5, since, in Case 4, a marked clinical improvement took place with the test becoming less strongly positive and finally negative. A trend towards becoming negative, or several negative readings, are of good omen. In these cases where the results fluctuated from negative to various degrees of positivity, the outcome is presumably still in doubt.

An interesting case is number 12. This was a woman who was very upset and deteriorated clinically on learning of a motor accident to her husband while on his way to visit her ; her test became positive within a few days, remaining so for two further weeks and became negative again at the end of a month.

Duration.—The relationship of the test to the duration of the disease is shown in Fig. 1. It will be seen that all the observations in cases of under six months' duration were negative ; in cases of six to eleven months' duration there were two which had negative and two which had positive results ; in Cases of one to three years' duration only ten had negative tests, whereas eighteen had positive, a ratio of nearly 1 : 2. In cases of over three years' duration, there were nearly equal numbers of positive and negative results.

It is concluded that most cases tested in the first six months of the disease will be negative, and that thereafter, there will be an increasingly greater number of positive results until about the third year, from which time onwards the numbers of negative and positive results will be approximately equal.

TABLE 5

BLOOD SEDIMENTATION RATES

Test results	Blood sedimentation rates in mm.			
	0-9	10-29	30-49	over 50
Negative	16	41	19	24
Positive	9	30	20	41

TABLE 6

RADIOGRAPHIC APPEARANCES

x-ray results	Gold results	
	Negative	Positive
Normal	7	2
Early changes of rheumatoid arthritis	14	15
Marked changes of rheumatoid arthritis	6	6
Advanced changes of rheumatoid arthritis	8	14

Sedimentation Rate.—Table 5 shows the number of blood sedimentation rates (BSR) associated with positive and negative gold results. It will be seen that there is a definite tendency for a low BSR to be associated with a negative gold and a high BSR with a positive one. On the other hand, there is clearly no absolute relation between the two tests, since both a normal and an elevated BSR have been found with either a positive or a negative gold test, as can be seen from the table. That is to say, whatever the circumstances are which determine the rate of sedimentation, they are not the same as those which determine the gold reaction, since the two results can be dissociated.

Degree of Arthritis.—The degree of arthritic change was assessed from the radiographs, which were available in every case. The appearances of the radiographs were classified as being normal, or showing the early, marked, or advanced changes of rheumatoid arthritis. Table 6 shows that the damage done is not related to the gold reaction except in so far as the early cases with no *x*-ray changes gave predominantly negative gold tests.

Gold Therapy.—Seven persons were under treatment with myochrysine during the period of observation, too small a number from which to draw any conclusions ; the tests of four remained negative, two became less positive, and one changed from negative to positive and back again to negative. Fifty-seven cases had had gold therapy at some time prior to admission, and of these, thirty had a positive and twenty-seven a negative test.

Muscle Biopsy.—A muscle biopsy was performed on twenty-six cases ; no relationship was found between these results and the gold test.

Discussion

In this series, 51 per cent. of the cases gave a positive gold reaction on at least one occasion. Higher figures have been given elsewhere ; 76 per cent. (Carter and Maclagan, 1946), 71 per cent. (Rennie and Rae, 1947), and 61 per cent. (Fraser, 1948). None of these workers stated whether the cases were early or late, active or inactive. It may be that the explanation of the smaller percentage in this series is that earlier and less seriously affected cases were available for examination.

Like Fraser (1948), no relationship was found between the results of the test and the age at examination, sex, and degree of arthritic change. His statement, however, that there is a definite relationship between the results of the test and the blood sedimentation rate can only be accepted with reservations since it has been shown that, while there is admittedly a tendency for a low BSR to be associated with a negative gold, and a high BSR with positive gold, the two can be completely dissociated ; they must, then, be due to different mechanisms, and therefore impart different information. It has been shown, by Ham and Curtis (1938), that the BSR can be influenced by (*a*) changes in the red cells, and (*b*) quantitative changes of the plasma proteins. A decrease or an increase of any of the plasma proteins may cause a change in the BSR, but unless that change happens, for the time being, to be the same as that causing a positive gold reaction, the two tests will not run in parallel.

The serum protein changes responsible for a positive gold test were first thought to be purely quantitative, resulting in a reversed albumin/globulin ratio. Gray (1940), however, showed that this was not so, since positive results could be obtained in the presence of a normal globulin level and a normal albumin/globulin ratio, while negative results could occur with an elevated globulin ratio and a low or inverted albumin/globulin ratio. In 1942 Gray further showed that the test depended upon the gamma globulin fraction; by adding increasing amounts of electrophoretically pure gamma globulin to serum, he found that the test became increasingly positive, whilst the addition of electrophoretically pure albumin inhibited this. This has since been confirmed by Kabat and others (1942), who also showed (1943) that the test depends on qualitative as well as quantitative changes, in that different albumin preparations vary in their inhibitory power. Maclagan and Bunn (1947) showed that the alpha and beta globulins could also inhibit the reaction.

Electrophoretic studies of twenty-three cases of rheumatoid arthritis were made by Perlmann and Kaufman (1946) and in one case by Dole and Rothbard (1947). The former found that the alpha globulins became elevated early in the disease and the gamma globulins later. This might explain why the gold test is negative in the first six months or so, and when the gamma globulins become elevated later, the test may become positive. An explanation of why so many cases continue to give a negative reaction while just as clinically active as those giving a positive one, may well be that the effect of the elevated gamma globulins (if indeed they are always raised) is inhibited because one or other of the albumin, alpha, or beta fractions is also elevated sufficiently to inhibit the reaction.

Speculation as to why gamma globulins are increased in this disease is outside the scope of this paper, but three theories may be mentioned.

1. That the serum antibody level is raised in response to some unknown antigen, since it is known that some antibodies are attached to the gamma fraction (Enders, 1944).

2. That the liver is damaged and, by analogy with other conditions with liver damage, it is unable to break down the complex " storage " protein of high molecular weight, to the simpler albumin of small molecular weight, finding it easier to produce gamma globulin which has a large molecule (Wilensky, 1946).

3. That an abnormal protein, resulting from synovial or other articular damage, is circulating in the blood and is of the same order of molecular weight and electrophoretic mobility as the gamma globulins (Perlmann and Kaufman, 1946).

Whatever the true explanation may be, there is clearly need for further investigation of the serum protein fractions in rheumatoid arthritis, using a more direct method of measuring them than by the indirect means of showing a relatively increased serum level offered by the colloidal gold reaction. When this has been done in a similar series, it may be possible to explain the significance of this elevated gamma globulin.

Summary

1. The results of the colloidal gold test were studied in a series of seventy-two cases of rheumatoid arthritis of all degrees of activity, in which the age and sex incidence corresponded with that of other published series, and it was therefore considered to be a representative one.

2. Three types of result were obtained ; those always positive, those always negative, those which were sometimes one and sometimes the other ; and it was concluded that a single test was of no value in assessing clinical activity.

3. Repeated tests were of value in estimating progress and prognosis in that consistently negative tests, or tests tending to become less positive indicated a good prognosis ; repeatedly strong tests, particularly if more than one 5 were obtained, indicated a bad prognosis ; and tests which were sometimes positive and sometimes negative probably indicated that the outcome of the disease was still undecided.

4. It was shown that the disease had to be at least of six months' duration before the test became positive, and that for the next three years it was twice as often likely to be positive as negative ; thereafter, it was equally likely to be positive as negative.

5. It was demonstrated that the blood sedimentation rate and the gold test were unrelated, although frequently the causative mechanisms for each might simultaneously be in action so that the results might run in parallel.

6. No relationship was found between the results of the test and the age and sex of patients, the degree of arthritic change, or the gold therapy given.

7. It was shown from the literature that the test probably depended upon an elevated serum gamma globulin, but that it could be inhibited by sufficiently elevated serum albumin, alpha, or beta globulins. It was suggested that the explanation of persistently negative results in clinically active cases was that the reaction was being masked by one or more of these other fractions being also elevated.

The muscle biopsies and their histological examination were undertaken by Dr. B. Cruickshank, to whom I am indebted. I should also like to acknowledge my debt to Dr. J. J. R. Duthie, whose helpful criticism I found very valuable.

References

Carter, A. B., and Maclagan, N. F. (1946). *Brit. med. J.*, **2**, 80.
Dole, V. P., and Rothbard, S. (1947). *J. clin. Invest.*, **26**, 87.
Enders, J. F. (1944). *Ibid.*, **23**, 510.
Fraser, T. N. (1948). *Annals of the Rheumatic Diseases*, **7**, 83.
Gray, S. J. (1940). *Arch. int. med.*, **65**, 524.
—— (1942). *Proc. Soc. Exp. Biol., N.Y.*, **51**, 400.
Ham, T. H., and Curtis, F. C. (1938). *Medicine*, **17**, 447.
Kabat, E. A., Moore, D. H., and Landow, H. (1942). *J. clin. Invest.*, **21**, 571.
——, Hanger, F. M., Moore, D. H., and Landow, H. (1943). *Ibid.*, **22**, 563.
Maclagan, N. F. (1944). *Brit. J. exp. Path.*, **25**, 15.
——, and Bunn, D. (1947). *Biochem. J.*, **41**, 580.
Perlmann, G. E., and Kaufman, D. (1946). *J. clin. Invest.*, **25**, 931.
Rennie, J. B., and Rae, S. L. (1947). *Brit. med. J.*, **2**, 1030.
Sclater, J. G. (1943). *Annals of the Rheumatic Diseases*, **3**, 195.
Westergren, A. (1926). *Amer. Rev. Tuberc.*, **14**, 94.
Wilensky, A. O. (1946). *Arch. Surg.*, **48**, 36.

Valeur des Réactions a l'or Colloidal Répétées dans l'Arthrite Rhumatismale

Résumé

Les résultats des réactions à l'or colloidal furent étudiés dans une série de soixante douze cas d'arthrite rhumatismale à tous les dégrés d'activité ; l'incidence de l'âge et du sexe y correspondait à celle des autres séries

publiées ; cette série peut donc être considérée comme représentative.

Trois types de résultats furent obtenus : les toujours positifs, les toujours négatifs et ceux qui étaient parfois l'un et parfois l'autre ; on conclut qu'une seule réaction était sans valeur pour déterminer l'activité clinique.

Les réactions répétées se sont montrées utiles pour évaluer le progrès et le pronostic ; ainsi les réactions constamment négatives ou celles qui tendaient à devenir moins positives indiquaient un pronostic favorable ; des réactions fortes répétées, surtout lorsqu'on obtenait plus d'un 5, indiquaient un pronostic mauvais ; et les réactions parfois positives et parfois négatives indiquaient probablement que l'évolution de la maladie n'était pas encore décidée.

Il fut démontré que la maladie devait être là depuis six mois au moins pour que la réaction devienne positive et que pendant les trois années suivantes il y avait deux chances sur une qu'elle soit positive plutot que négative ; plus tard les chances devenaient égales.

Il fut démontré qu'il n'y avait pas de rapport entre la sédimentation globulaire et la réaction à l'or, bien que souvent les mécanismes respectifs en cause pouvaient agir en même temps créant ainsi une évolution parallèle.

On n'a pas trouvé de rapport entre les résultats de la réaction et le sexe des malades, le dégré des changes arthritiques ou l'intensité de la chrysothérapie.

On a montré, en se basant sur la littérature, que la réaction dépendait probablement de la gamma globuline du serum mais qu'elle pouvait être inhibée par l'albumine, par l'alpha- ou par la beta-globuline suffisamment élevées. On a suggéré que les résultats négatifs persistants dans des cas cliniquement actifs s'expliquaient par le fait que la réaction étaient masquée par l'augmentation simultanée d'une ou de plus de ces fractions.

SEVENTH INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES

This Congress, the first to be held under the auspices of the Ligue Internationale contre le Rhumatisme since the war, was held in New York from May 30 to June 3, under the chairmanship of Dr. R. Freyberg, President of the American Rheumatism Association, who were hosts. After this, a large party of delegates visited the Annual Meeting of the American Medical Association in Atlantic City, and were afterwards taken on a tour of some of the leading centres of rheumatism research in the United States. These included Philadelphia, Boston, Buffalo, Ann Arbour, Chicago, The Mayo Clinic, and Washington, D.C. Some 600 delegates attended from no less than 26 nations ; at the inaugural meeting the audience numbered over 1,000, as it did at the session to which the paper by Drs. Hench, Kendall, Slocumb, and Polley was read, in which they officially announced the remarkable results they had obtained by the use of " Cortisone " (their original report was published in our last number). Five other distinguished physicians had been given 1 gramme of this substance for independent trial and they all personally confirmed similar results. These were Drs. R. Freyberg, E. Boland, P. Holbrook, E. Rosenberg, and Walter Bauer.

At the official banquet the following foreign rheumatologists were presented with Honorary Membership of the American Rheumatism Association.

Lord Horder (London, England), Dr. Charles W. Buckley (Buxton, England), Dr. George D. Kersley (Bath, England), Dr. R. G. Gordon (Bath, England), Dr. J. Barnes Burt (Bath, England), Dr. William Tegner (London, England), Dr. J. A. Glover (London, England), Dr. W. S. C. Copeman (London, England), Dr. Douglas H. Collins (Leeds, England), Prof. L. S. P. Davidson (Edinburgh, Scotland), Dr. Anibal Ruiz-Moreno (Buenos Aires, Argentina), Dr. P. Barcelo (Barcelona, Spain), Dr. Thore Gunnar Kahlmeter (Stockholm, Sweden), Dr. Gunnar Edström (Lund, Sweden), Dr. Frederik Sundelin (Nyashamn, Sweden), Dr. Jacques Forestier (Aix-les-Bains, France), Dr. Matthieu Pierre Weil (Paris, France), Dr. J. van Breemen (Amsterdam, Holland), Dr. Med. Knud Brochner-Mortensen (Copenhagen, Denmark), Prof. Dr. Med. Cai Holton (Aarhus, Denmark), Dr. Ejnar V. Jarløv (Copenhagen, Denmark), Dr. Svend Clemmesen (Copenhagen, Denmark).

Some of these gentlemen were also elected to the Honorary Membership of the Danish Rheumatism Society.

At a meeting of the Ligue Internationale contre le Rhumatisme, held during the Congress, the following officers were elected for the next four years. President : Professor J. Jarløv (Denmark) ; Secretary General : Dr. W. Tegner (England) ; Treasurer : Mr. O. de Bornemann. President of the European Branch : Dr. W. S. C. Copeman (England) ; Secretary : Dr. G. Edström (Sweden) ; Treasurer : Mr. O. de Bornemann. The Honorary Membership of the Ligue was conferred upon the retiring Secretary General, Dr. J. Van Breemen (Holland), Professor Ralph Pemberton, who unfortunately died suddenly a few days later (an obituary notice appears at p. 256 of this issue), and Dr. Loring Swaim, who deputized for Dr. Pemberton throughout.

Over one hundred papers were read and five " panel " discussions were held. The standard of all these was exceptionally high and the Congress would have been a notable one even if the recent work on the adrenal and pituitary hormones had not been presented. The thanks of all who attended are due to the hosts, who must have worked untiringly for many months previously to render the Congress so successful in every aspect.

The proceedings are being published by the American Rheumatism Association towards the end of the year, and this *Journal* proposes by agreement with them, to publish a series of abstracts of certain of the most important papers together with certain of the other papers in full, of which only an abstract will appear in the Proceedings.

Of the organization of the social side we have nothing but praise. Lavish hospitality and kindness were enjoyed by all the delegates.

The next Congress (European) will be held in Spain in 1951, with a further International Congress in America again two years later.

ABSTRACTS

[This section of the ANNALS *is published in collaboration with the two abstracting Journals,* Abstracts of World Medicine, *and* Abstracts of World Surgery, Obstetrics and Gynaecology, *published by the British Medical Association. The abstracts are divided into the following sections: acute rheumatism; chronic articular rheumatism (rheumatoid arthritis, osteo-arthritis, spondylitis, miscellaneous); sciatica; gout; non-articular rheumatism; general pathological articles; other general articles. At the end is a list of articles that have been noted but not abstracted. Not all sections may be represented in any one issue.]*

Acute Rheumatism

Acute Rheumatism and Treatment of its Prolonged Forms by Intra-arterial Injections of Streptococcus-Enterococcus "Anavaccine". (A propos de la maladie de Bouillaud et du traitement de ses formes trainantes par des injections intra-artérielles d'ana-vaccin strepto-entérocoque.) DEBRAY, M., and PROVENDIER, M. (1948). *Sem. Hôp. Paris*, **24**, 2325.

The authors attempt to evoke a local immunity by bringing an antigen into direct contact with the arterial tissues. The antigen used they call an anavaccine; it is a lysate of streptococci, enterococci, and staphylococci. It is injected slowly into the femoral artery, at intervals of 4 to 7 days. Injections are followed by a slight rise in temperature, and in some patients by a blanching of the fingers resembling the Raynaud phenomenon and lasting 1 to 1½ hours. No serious reactions were encountered in several hundred intra-arterial injections in patients with Bouillaud's disease. Vaccine injections are not begun until acute symptoms have abated under salicylate therapy. The authors think the method is of special value in prolonged or relapsing types of the disease. They think it too early to say that the prognosis can be modified in this way, but believe that the clinical effects they record are worthy of attention. *Kenneth Stone.*

Studies on the Agglutinins Against Haemolytic Streptococci in Rheumatic Diseases. [In English.] WINBLAD, S., and EDSTRÖM, G. (1948). *Acta path. microbiol. scand.*, **25**, 715.

The authors point out that there are two types of agglutination; in one the antigen appears in non-encapsulated living streptococci and disappears after the organisms have grown for more than 14 hours, or after shaking and centrifugation, this being termed "L agglutination"; in the other an antigen occurs in autoclaved haemolytic streptococci and is termed by Thulin "O-antigen". The authors studied L agglutination of Group A type I haemolytic streptococci suspended in a special broth (formula given) by a series of 206 sera from cases of rheumatoid arthritis (nearly all cases being tested repeatedly), a control series of 105 normal sera, and 72 sera from cases of rheumatic fever. The inactivated serum, serially diluted with 0·3% NaCl to titres up to 1 in 640 is incubated for 2 hours at 52° C. after addition of an equal broth suspension, and the result read after leaving overnight in the refrigerator. Three degrees of positive agglutination are recognized, particle and clump formation being considered positive. Positive agglutination (beyond a titre of 1 in 10) developed in 68% of sera from cases of rheumatoid arthritis compared with 6% of the control sera, and there was a significant correlation with the rate of erythrocyte sedimentation. In rheumatic fever, 35% of sera gave a positive agglutination: 5 individual charts are shown. It appears that the agglutination titre becomes raised several months after the acute stage (22% were positive up to 4 months, whereas 47% of the sera were positive after 4 months from the onset). Three explanations are offered to account for these findings: (1) The late positive reaction results from a continuing streptococcal infection. (2) The streptococcus may change after a period and produce this different late antigen (the most feasible explanation according to the author). (3) The reaction is a non-specific flocculation reaction such as is seen with collodion particles (Wallis). *E. G. L. Bywaters.*

Comparison of Salicylate Therapy by Mouth, Intravenously, and with a Retarding Agent in Acute Rheumatism. (Comparaison de la salicylothérapie "per os" intraveineuse, et retard, dans la maladie de Bouillaud.) CAMELIN, A., PELLERAT, J., MURAT, —, and MAGERAND, M. F. (1948). *Lyon Médical*, **18**, 605-611.

A concentrated artificial plasma "subtosan 25" was used to maintain a high salicylate level in the blood in the treatment of acute rheumatism by the administration of sodium salicylate intravenously. A 5% solution of sodium salicylate in 10% glucose was given, with the addition of 10 ml. subtosan 25 to each dose. Twenty-five patients were treated with 6 to 9 g. daily, given in two or three doses at 8- or 12-hourly intervals. It is claimed that a satisfactory salicylate level in the blood of 175 to 200 mg. per litre was thus maintained. No toxic symptoms occurred and sclerosis of the veins did not develop, even after 3 weeks' treatment by this method. The authors state that the salicylate is also fixed in the tissues, particularly the myocardium, at a much higher level than after oral administration of the drug, and that the method is useful in salicylate-resistant patients. It is impossible to decide if there is any advantage in the method here described. *T. G. Reah.*

Salicylate Tolerance and Toxicity in Children. DUBOW, E., and SOLOMON, N. H. (1948). *Pediatrics*, **1**, 495.

Nineteen children ranging in age from 8 months to 11½ years were treated with sodium salicylate or acetylsalicylic acid in doses of either 0·10, 0·125, or 0·15 g. per kilo body weight per day. Six patients, from 3 to 11½ years old, were given 0·15 g. per kilo body weight daily. Five showed toxic symptoms—hyperpnoea,

apathy and lassitude, anorexia, and tinnitus. Administration of the drug was stopped before more severe toxic symptoms occurred. Plasma salicylate levels in these cases ranged from 32 to 41 mg. per 100 ml. The one child who showed no toxic symptoms on this dosage was afebrile and convalescent when treatment started. Acetylsalicylic acid appeared to be more toxic than sodium salicylate. An early fall in serum carbon dioxide content, followed by a gradual further fall, was noted ; blood *p*H rose at first, falling gradually later. The urine contained albumin, casts, red and white blood cells, and acetone. Gerhardt's test was positive constantly ; reduction of Benedict's solution was noted occasionally. When the dose of salicylate was reduced to 0·10 g. per kilo body weight daily, plasma salicylate values averaged only 20 mg. per 100 ml., well below the advocated therapeutic level of 35 mg. per 100 ml. With the intermediate dose of 0·125 g. per kilo body weight daily, plasma salicylate values ranging from 30·9 to 39·4 mg. per 100 ml. were obtained. None of the children receiving his dose showed any symptom of toxicity after prolonged administration, and serum carbon dioxide content and blood *p*H values were normal. In infants and children under 3 years of age therapeutic plasma levels were not reached with doses of sodium salicylate up to 0·15 g. per kilo. *P. T. Bray.*

Phenylethylhydantoin in the Treatment of Sydenham's Chorea. KIRK, T. R. (1948). *N.Y. St. J. Med.*, **48**, 2165.

This paper adds nothing to existing knowledge of the use of nirvanol in chorea. The rare but unpredictable disasters which occur are a deterrent to the use of a dangerous symptomatic remedy in a self-limited disease. *C. E. Donaldson.*

The Nutritional State of Children with Chronic Rheumatic Heart Disease. BENN, J. (1948). *Arch. Dis. Childh.*, **23**, 171.

It is concluded that, "Rheumatic heart disease probably has no inhibiting effect on the growth of children once the infection has subsided. The type of rheumatic infection and the presence of cardiac enlargement are also without effect."

Some Factors Predisposing to Juvenile Rheumatic Fever in Sydney. STOREY, J. (1948). *Med. J. Aust.*, **1**, 492.

This paper reports a survey of juvenile rheumatic fever carried out at the Royal Alexandra Hospital for Children in Sydney in 1946-7. The author states that the person most likely to develop rheumatic fever would be a child between the ages of 4 and 12 years, with a family history of the disease, living in an over-crowded area, and exposed to group A haemolytic streptococcal infection. *W. S. C. Copeman.*

Immunologic and Biochemical Studies in Infants and Children with Special Reference to Rheumatic Fever. II. Complement Titers in Normal Conditions. DE GARA, P. F., and GOLDBERG, H. P. (1948). *Pediatrics*, **2**, 242.

The authors examined 107 normal healthy children for complement titre, using the 50% haemolysis method. Of the 128 serum samples examined, 83% lay between 0·0040 ml. and 0·0069 ml. complement titre ; 6·3% had higher and 10·2% lower values. The values obtained did not vary with age, sex, or season of the year, nor did repeated samples from the same subject show any significant variation. *C. L. Oakley.*

Immunologic and Biochemical Studies in Infants and Children with Special Reference to Rheumatic Fever. III. Complement Titers in Abnormal Conditions. DE GARA, P. F., and GOLDBERG, H. P. (1948). *Pediatrics*, **2**, 248.

For comparison 421 samples from a mixed collection of 330 children, either suffering from or convalescent from illnesses, supposedly susceptible to rheumatic fever or suffering from it, were examined for complement titre. No evidence was found that recent illness alters the complement titre, though 25% of 75 normal children had low values during intercurrent non-rheumatic illnesses. A similar proportion of children suffering from acute rheumatic fever had low values. No evidence was obtained that complement activity is a factor in hereditary susceptibility to rheumatic fever. *C. L. Oakley.*

Oxygen Therapy in Acute Rheumatic Carditis in Children. TARAN, L. M., and SZILAGYI, N. (1948). *Amer. J. Med.*, **5**, 379.

Heart disease may diminish arterial oxygen tension and so reduce the oxygen supply to body tissues and disturb cell metabolism, including that of heart-muscle cells. Inhalation of an oxygen-enriched atmosphere containing 40 to 60% oxygen may improve the oxygenation of the heart muscle in such cases. The value of inhaling an oxygen-enriched atmosphere in heart disease was explored previously by Barach and his associates, who considered it of less value in inflammatory than in degenerative heart disease, and by Pouton, who found improvement in acute rheumatic carditis.

The authors discuss the results of 2 years' work on 44 children, and support Poulton's views. Two special chambers were constructed in which 3 children at a time were observed continuously (except for *x*-ray examination) for an average time of 12 weeks in an atmosphere of 45 to 50% oxygen and 1·3 to 1·5% carbon dioxide at 66 to 68° F. and 60 to 70% humidity. Circulation of the atmosphere was achieved by convection.

The 44 children treated are grouped as : (1) 24 with acute carditis whose response was favourable ; (2) 17 with acute carditis and fixed mechanical cardiac disability with unfavourable response ; (3) 3 who showed marked intolerance of the treatment and were classified as having "bronchitic" types of rheumatic cardiac disease. Progress of those who responded favourably was assessed under these headings. (1) Clinical. In 18 out of 24 the temperature became normal within 24 hours. Respiration in all cases improved immediately. Weight was gained by 22 out of 24 more rapidly than expected. Appetite increased irrespective of the course of the disease. The colour of the face improved in most cases independent of any change in haemoglobin value.

Almost all showed rapid improvement in behaviour pattern. (2) Cardiac. The pulse rate was reduced in all cases from 110-130 to 70-90 in 24 hours. (This is the most significant finding recorded in this paper if the view is held that an actively inflamed heart will suffer the more damage the more rapidly it beats.) Clinical improvement in carditis was measurable in all cases. Changes in murmurs indicative of improvement were noted in some cases. All 7 patients with anginal pain together with ST segment changes in the electrocardiogram showed marked improvement. In the electrocardiogram conduction disturbances, ST segment changes and Q–T interval all showed changes commonly interpreted as indicating improvement. (The authors recognize that the above criteria are not absolute indications of the value of oxygen therapy because the natural history of the disease will not allow rigid comparisons.) (3) Rheumatic activity. The natural history of the disease was not significantly altered by oxygen therapy. *John Anderson.*

Effect of Oxygen Therapy on the Electrical Sequence of Events in the Cardiac Cycle in Children with Acute Rheumatoid Carditis. TARAN, L. M., and SZILAGYL, N. (1948). *Amer. J. Med.*, **5**, 392.

The authors find that in acute rheumatic carditis the significant electrocardiographic finding was a lengthening of Q–T time which indicates prolonged cardiac contraction with a relatively unchanged T–Q time which indicates curtailed cardiac relaxation in diastole. As it is during diastole that myocardial cellular balance is restored it seems that such curtailment may aggravate the acute carditis. These abnormalities run parallel to the clinical state, and when they are present for a prolonged time various rhythm disturbances develop or cardiac dilatation or hypertrophy with objective signs of heart failure. It is suggested that oxygen therapy in the early acute phase of carditis (called the stage of anoxia by the authors) may favourably influence the course of the disease by prolonging the rest period. It was shown that oxygen therapy diminished the heart rate and restored the normal relation of Q–T to T–Q intervals. Previously the authors showed that recovery of carditis is accompanied by shortening of the Q–T interval with an unaltered T–Q period. They now show that with oxygen therapy the Q–T time remains unaltered while the T–Q time is prolonged ; in either event the normal relation between Q–T and T–Q is restored, though by different mechanisms. This prolongation of T–Q is achieved without increasing conduction delay. It is postulated [reasonably] that the chemical economy of the heart is assisted by the longer diastole and that such assistance may prevent further damage to the heart during acute carditis.

The authors use a graphic method to express Bazette's formula (which states that $K=\frac{\text{Q–T time in seconds}}{\text{cardiac cycle in seconds}}$ where the upper limit of K in normal children is 0·405) and illustrate their text to bring out these points. [These papers contain much useful information.] *John Anderson.*

Ventricular Escape in Acute Rheumatism. KIRBY, A. C. (1948). *Brit. Heart J.*, **10**, 234.

Two children with acute rheumatism and carditis in which abnormal rhythms were recorded are described. One, aged 11, with moderate carditis, showed a rhythm in which the ventricle responded to impulses from the auriculo-ventricular node at a rate of 107 per minute ; the auricle beat independently at 83 per minute. The abnormal rhythm appeared to last 2 days. The child recovered. The second, a girl aged 8, had acute carditis which was progressive even though under treatment. After several weeks there was an attack of dyspnoea and her colour became ashen grey ; the pulse rate rose to about 150 and was irregular. The cardiogram showed a rate of about 150 with P and T waves superimposed ; P gradually approached the previous QRS, and when they became contiguous there was a longer cycle ; the following P wave preceded QRS by 0·2 second. Later congestive failure appeared, but the heart rate was slower and a sinus rhythm with a P–R interval of 0·2 second was recorded. The child died, and at necropsy there was evidence of pancarditis.

[In Case 2 the correct interpretation of the abnormal rhythm would appear to be partial auriculo-ventricular block showing the Wenckebach phenomenon ; in Case 1, in which the auriculo-ventricular node does control the ventricles at times, the rhythm, though it may be described as ventricular escape, also resembles nodal tachycardia, although in this the auricles also are usually controlled by the auriculo-ventricular node. Occasional ventricular responses to a sinus impulse are shown in Fig. 1 of the paper as indicated by slight alterations in cycle length and in the shape of the ventricular complex. Probably the focus which controls the ventricles is situated in the lower part of the auriculo-ventricular node.] *S. H. Cookson.*

A Case of Rheumatic Heart Disease with Periodic Arterial Embolism : Ambulatory Treatment with Dicumarol. SPRAGUE, H. B., and JACOBSEN, R. P. (1948). *Med. Clin. N. Amer.*, **32**, 1309.

A man, aged 38, had mitral regurgitation and stenosis of rheumatic origin, with auricular flutter. He had repeatedly had arterial embolism. An embolus, lodged in his left femoral artery, was successfully removed and 2·2 g. of heparin was given intravenously in 5 days. Subsequently dicoumarol was given daily for nearly a year, the patient remaining ambulatory. The dosage was controlled by determination of the prothrombin time by Quick's method. Dicoumarol administration was begun in the usual manner, 300 mg. being given the first day, 200 mg. the next day, and 100 mg. thereafter. A maintenance dose of 50 mg. daily was used. With this a prothrombin time of 50 to 60 seconds was maintained. Slight nasal bleeding was taken as a sign of overdosage since it occurred when the prothrombin time was nearly 80 seconds. *F. A. Langley.*

Significance of Electrocardiographic Changes in Rheumatic Fever. SOKOLOW, M. (1948). *Amer. J. Med.*, **5**, 365.

Discussion is based on 700 personally observed cases of rheumatic fever, of which 147 (21%) had ECG

abnormalities. The latter are grouped as follows: (1) Conduction defect. Eighty-eight out of the 147 abnormalities were conduction defects—partial A–V block, complete A–V block, and intraventricular block. These changes are usually transient. A P–R interval of 0·2 to 0·22 second is taken as normal, but with rapid heart rates shorter P–R intervals represent normality. Serial records which show a shortening of P–R interval of more than 0·04 second are taken as evidence of transient conduction defect. In 4% of cases with prolonged conduction time the change was fixed over a period of months, and the authors suggest that this may mean that the isolated prolongation of conduction time found in normal aviators may be due to rheumatic carditis. (2) T-wave changes. Of the 147 abnormalities 52 took the form of inverted or diphasic T waves in leads I, II, and IV in the absence of clinical pericarditis. It is emphasized that serial electrocardiograms may show that an isolated pattern which could be accepted as normal is in fact abnormal. The mechanism of these T wave changes is uncertain, but they are similar to experimentally produced subepicardial inflammatory changes in the ECG. (3) Miscellaneous changes. Twenty-six of the abnormalities consisted of abnormal rhythms, inverted P waves (P_2, P_3), or alterations in electrical axis, but these changes were rarely isolated and were not accepted alone as evidence of carditis. Auricular fibrillation was rare. Inflammatory foci in the myocardium may be responsible for the abnormal origin of stimuli and P wave inversion. Where the ECG and clinical findings disagree observation of progress is necessary to decide whether carditis is active or whether the ECG changes represent old inactive disease and scarring of the myocardium.

John Anderson.

Serial Electrocardiographic Changes in Young Adults with Acute Rheumatic Fever; Report of 62 Cases. BLACKMAN, N. S., HAMILTON, C. I. (1948). *Ann. intern. Med.*, **29**, 416.

In 62 soldiers, aged 17 to 21, admitted to hospital for acute rheumatic fever, serial electrocardiograms were taken every other day during the first week and twice a week thereafter until the patient's discharge for convalescence. The limb leads and lead CF_4 were taken, and lead III was taken during normal respiration and again during held inspiration. Changes were determined by the limb leads alone. Only one case showed entirely normal records throughout. The most important changes were: alterations in T waves and ST segments in 38 cases; first-degree auriculo-ventricular block in 26; prolongation of the Q–T interval in 22 ($K\sqrt{\text{cycle}}$ exceeding 0·4 second); elevation or depression of ST segments in 14; S_1, Q_3 pattern in 7; inversion of T waves in limb leads in 7; S_2 greater than 3 mm., without axis deviation, in 7. It is emphasized that a larger number showed changes in final deflections than lengthening of P–R intervals, and that the return to normal of the electrocardiogram cannot be accepted as indicating complete remission of rheumatic activity.

(The authors' method for determining axis deviation seems unusual. Case 5, interpreted as showing a wandering pacemaker, may well have been one of dissociation with interference.) *A. Schott.*

The Aetiology and Pathogenesis of Acute Rheumatism. (Kotázke etiologie a patogenezy akútneho reumatizmu.) BROZMAN, M. (1948). *Brátislavské lekárs. Listy*, **28**, 691.

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

Chrysotherapy and its "Toxic" Reactions in Rheumatoid Arthritis. [In English.] EDSTRÖM, G. (1948). *Acta med. scand.*, **131**, 571.

Thirty-three patients were treated with "solganol B oleosum" (aurothioglucose) or "neosolganol" (aurokeratinate) and the gold content of plasma and urine was serially estimated. In 8 toxic phenomena developed; of these, 6 had dermatitis (2 severely exfoliative), 1 aphthae and mild diarrhoea, and 1 albuminuria. No relation was found between concentrations of gold in plasma or size of dose and the presence or absence of toxic reactions. It is concluded that the latter are an expression of hypersensitiveness, and that they cannot be avoided. BAL was beneficial. [No mention is made of any relation between toxic reactions and duration of treatment.] *Bernard Freedman.*

Primary Splenic Neutropenia with Arthritis (So-called Felty's Syndrome). Its Treatment by Splenectomy. SMITH, S., and MCCABE, E. S. (1948). *Ann. intern. Med.*, **29**, 445.

In one of the two cases reported there was hypoplastic bone marrow. Splenectomy appeared to restore the blood condition to normal and also undoubtedly improved the patient's self-confidence and resistance to infection, but the authors do not stress the value of this operation as regards arthritis. [Similar observations were made by Steinberg (*Ann. intern. Med.*, 1942, **17**, 26). "Chronic Arthritis in the Adult, Associated with Splenomegaly and Leucopenia" is the title of a short article by Felty in the *Bulletin of the Johns Hopkins Hospital*, 1924, **35**, 16. The condition was briefly reviewed in the *British Medical Journal*, 1940, **2**, 636.] *G. F. Walker.*

(Spondylitis)

Unilateral Sacro-iliac Arthritis as a Form of Onset of Spondylitis Ankylopoietica. (Sacroileitis unilateral como forma de comienzo de la espondiloartritis anquilopoyética.) BOIXET, E. B., and QUEROL, J. R. (1948). *Rev. esp. Reum.*, **2**, 488.

The authors accept the statements that ankylosing spondylitis starts in the sacro-iliac joints and that it is nearly always bilateral and gives rise to no specific symptoms. [That is contrary to some recent views that the early changes are in the intervertebral facets—diminution in joint space and para-articular osteoporosis.] They think, however, that in the early stages spondylitis probably causes symptoms referable to the sacro-iliac joints; these symptoms disappear when the

joint becomes rigid. They thus regard the diagnosis of the disease as possible in the early stages, the difficulty being to distinguish it from cases of infective sacro-iliac arthritis due to tuberculosis and typhoid fever. Four cases are described, all with symptoms and radiological signs of unilateral sacro-iliac arthritis ; in 3 cases the arthritis became bilateral and there were subsequent signs of spondylitis. The interval between the first sacro-iliac signs and those in the vertebrae may be 5 to 6 years. The authors think that patients are rarely seen in the stage of unilateral disease ; they also think that oblique *x*-ray films may be of some help and they stress that when unilateral sacro-iliac changes are present spondylitis should be thought of as a possibility.

Paul B. Woolley.

Results of Surgical Correction of Bony Ankylosis with Deformity in Spondylitis. Six Observations. (Résultat du redressement chirurgical des ankyloses osseuses vicieuses des spondylarthrites d'après six observations.) HERBERT, J. -J. (1948). *Rev. Rhum.*, **15**, 250.

This paper reports 6 cases of osteotomy of the spine for deformity due to ankylosing spondylitis. The longest period over which any case has been studied since operation is 18 months. In 5 cases the osteotomy was performed posteriorly only, and simple redressement after the posterior bone section was sufficient to correct the deformity. In one case division of intravertebral disks was also necessary. The deformity appears to have been well corrected in all 6 cases. Two of the patients had troublesome but transient root pains in the thighs after the osteotomy. The author's criterion of a good result is the ability on the part of the patient to lie flat on his back with his calves, the lower part of his back, and the back of his head all in contact with a flat base board. The indications for the operation are discussed in some detail.

D. Ll. Griffiths.

(Miscellaneous)

Thrombocytopenic Purpura Complicating Gold Therapy for Rheumatoid Arthritis. Report of Three Cases with Spontaneous Recovery and one Case with Recovery following Splenectomy. METTIER, S. R., MCBRIDE, A., and LI, J. (1948). *Blood*, **3**, 1105.

Among 160 patients receiving gold salts for the treatment of rheumatoid arthritis, 4 developed thrombocytopenia and a haemorrhagic diathesis. In 3 the blood disorder was mild, and in 2 recovery was spontaneous when gold treatment was stopped ; 1 patient had a single blood transfusion of 500 ml. The fourth case was more serious, the complication occurring after repeated courses of gold ; there was continuous oozing from nose and gums and red cells appeared in the urine; ecchymoses and purpura appeared and there was at first some uterine haemorrhage. Four blood transfusions were given without effect. The sternal marrow was hyperplastic with increase in megakaryocytes. Splenectomy was therefore decided on and carried out successfully. The platelet count rose from 10,000 per c.mm. before operation to 210,000 per c.mm. 4 hours after operation ; 3 months later the platelet count as 550,000 per c.mm. There was no postoperative bleeding. This experience suggests that splenectomy may be worth while in the rare case which fails to respond to ordinary measures.

M. C. G. Israëls.

Arthralgic Leukemia in Children. [In English.] BICHEL, J. (1948). *Acta haemat., Basel*, **1**, 153.

This is a report of 3 cases of acute leukaemia in children in which the onset was accompanied by joint pains. The types of radiographic changes in bones that may be found in leukaemia in childhood are classified as follows : (1) Bone absorption often seen in the metaphyses of long bones as small scattered, usually elongated, areas of destruction, but which may be scattered over the whole bone, giving a worm-eaten appearance. Very fine streaky rarefaction may be the earliest stage. (2) Generalized osteoporosis, which may lead to spontaneous fractures and even gibbus, resembling Pott's disease. (3) Periosteal layering, seen as dense lines parallel to the shaft, sometimes ensheathing the whole bone in a lamellar manner. (4) A band of lessened density, a few millimetres wide, in long bones, parallel to the epiphyseal line. (5) Osteosclerosis. None of the appearances is pathognomonic of leukaemia.

A. Piney.

Denervation of the Elbow Joint for the Relief of Pain. A Preliminary Report. BATEMAN, J. E. (1948). *J. Bone Jt Surg.*, **30B**, 635.

Study of the innervation of 152 elbow-joints showed the following : the largest and most constant contribution comes from the ulnar nerve, usually as a single twig, often as two, and occasionally as several ; a less constant and smaller contribution is derived from the median nerve with some reciprocity with the ulnar nerve ; an occasional branch comes from the musculo-cutaneous nerve ; some twigs leave the radial nerve where it meets the radial and interosseous arteries, and some come from the plexus from the branch of the radial nerve to the anconeus muscle, lying in or beneath that muscle. At operative denervation the joint is approached through three incisions. The first is made between the biceps tendon and the medial epicondyle, exposing both median and ulnar nerves ; branches are identified 2 in. (5 cm.) above the joint and traced to the elbow ; one to three branches are found and severed. The second incision lies between the biceps tendon and the lateral epicondyle, where articular branches from the musculo-cutaneous nerve are divided beneath the biceps, and, deeper still, articular branches from the radial nerve near its bifurcation are severed. The third incision is made behind the lateral epicondyle over the anconeus muscle, where the nerve filaments together with a small vascular plexus are removed. In all cases the nerves are stripped ; the anatomical law that articular branches are supplied before muscle branches is found reliable.

Eleven patients were followed up for periods of from 4 to 21 months. Before operation they all had pain aggravated by use and persisting at night, and radiographic evidence of osteo-arthritis. After the denervation the sharp stabbing pain on movement had disappeared and sleep was undisturbed. The previous

range of movement was quickly regained, but forced movements caused discomfort. In all cases but one improvement was maintained and the patients returned to their former occupations. The development of a neurotrophic joint is considered unlikely by the author, as deep sensation passing along tendons and muscles is not interfered with. *J. C. R. Hindenach.*

The Innervation of the Shoulder Joint. GARDNER, E. (1948). *Anat. Rec.*, **102**, 1.

Because the intracapsular distribution of the nerves to the shoulder-joint has never been studied, the author re-investigated the nerve supply of the joint both macroscopically and microscopically, by dissecting eleven adult specimens and by preparing serial sections at 10 μ of four joints from 11-week and 12-week foetuses.

The joint is supplied by the circumflex and suprascapular nerves, the posterior cord of the brachial plexus, the stellate ganglion, and, less constantly, the lateral anterior thoracic and the radial nerves. The circumflex nerve gives off branches which supply the inferior, antero-inferior, and posterior-inferior aspects of the capsule. One twig ascends in the bicipital groove to the head of the humerus. The suprascapular nerve supplies the capsule on the superior, antero-superior, and postero-superior aspects of the joint. It sends twigs to the coraco-acromial ligament and the acromio-clavicular joint. The posterior cord of the brachial plexus gives off, close to its termination, a branch which divides. One twig supplies the anterior aspect of the capsule ; another joins a sympathetic filament which, arising from or near the stellate ganglion, descends in the adventitia of the axillary artery and reaches the joint by way of the articular branches of the latter. In about 40% of subjects the lateral anterior thoracic (lateral pectoral) nerve supplies the antero-superior part of the capsule and sends a twig into the joint by way of the bicipital groove. It also supplies the acromio-clavicular joint. In a small number of cases the radial nerve sends small twigs into the joint by way of the bicipital groove.

Within the substance of the joint capsule most of the nerves follow the vessels into the inner, synovial, vascular layer, and appear to be distributed to the vessels themselves, but some nerve fibres ramify in the outer fibrous layer of the capsule and probably terminate in endings of the Ruffini type ; these latter fibres are most numerous in the antero-inferior and antero-superior parts of the capsule, that is, in parts subject to great deformation during movement. *H. Hughes.*

The Innervation of the Elbow Joint. GARDNER, E. (1948). *Anat. Rec.*, **102**, 161.

This study is based upon the dissection of 7 adult elbow-joints and the examination of 10μ serial sections of 5 foetal joints.

The elbow-joint is supplied by the musculo-cutaneous, median, ulnar, and radial nerves. (1) The articular branch of the musculo-cutaneous nerve arises from the nerve to the brachialis muscle in the middle third of the arm. It descends on the medial edge of this muscle, passes deep to it, supplying humeral periosteum, and dividing into a variable number of twigs enters the anterior aspect of the capsule. Some filaments reach the synovial membrane. (2) The branch of the median nerve usually arises just above the pronator teres and supplies the capsule near the medial epicondyle. A branch may also arise from the anterior interosseous nerve to supply the postero-inferior part of the capsule along the lateral edge of the olecranon process. (3) The branch of the ulnar nerve usually arises behind the medial epicondyle but may come off much more proximally. It supplies the postero-medial region of the capsule and the ulnar collateral ligament. (4) The radial nerve has the most extensive distribution to the joint. One branch usually arises in the radial groove and descends in the lateral head of triceps. A second arises just proximal to the olecranon process and supplies the capsule in the olecranon fossa. A third arises from the ulnar collateral nerve just proximal to the medial epicondyle and supplies the capsule proximal to the olecranon process. A fourth arises from the radial nerve just after it pierces the lateral intermuscular septum and supplies the radial collateral and annular ligaments and the antero-lateral aspect of the capsule. A fifth arises as the radial nerve lies anterior to the joint and supplies the anterior region of the capsule.

Each nerve supplies therefore a definite region of the joint and of these the anterior has the richest supply. This is the region most subject to compression on movement. The regions overlap, and the nerves may vary in their course towards the joint. The articular branch of the musculo-cutaneous is the most constant both in course and in distribution. *H. Hughes.*

Narrowing of Intervertebral Foramina Resulting from Degenerative Vertebral Processes as a Cause of Neuralgic Pain in the Shoulder and Pelvic Girdle Areas and in the Limbs. (Die Einengung der Foramina intervertebralia infolge degenerativer Wirbelsäulenprozesse als Ursache von neuralgischen Schmerzzuständen im Bereich des Schulter- und Beckengürtels sowie der Extremitäten.) DUUS, P. (1948). *Nervenarzt*, **19**, 489.

Degenerative changes in the vertebra and the intervertebral disks have been studied by Schmorl and his pupils and described as " osteochondrosis ". That changes of this kind can produce neurological signs and symptoms is not a new finding. The author has observed some 50 cases, 6 of which are described ; all these suffered from " stiff neck ", pain in one or both arms, spreading towards the tips of the fingers, paraesthesiae, and increasing discomfort during the night if the cervical spine was affected ; osteochondrosis of the lumbar spine produced lumbago, pains spreading into one or both legs, and increased pain during the night.

In some of these cases no abnormal neurological findings were encountered, in others impairment of reflexes and hypoaesthesia or anaesthesia were found. *X*-ray examination revealed " osteochondrosis ", and oblique radiographs of the cervical or lumbar spine revealed narrowing of the intervertebral foramina. This narrowing of some foraminae is, in the author's

opinion, the characteristic and important pathological basis of the whole clinical picture, causing compression of the nerves passing through the foramina. None of the patients died, but examination of other necropsy material enabled the author to demonstrate the histological findings in cases of narrowed intervertebral foramina. He recommends a plaster-of-Paris jacket and administration of calcium and phosphorus.

[The histological findings are interesting, though the patients were very old (83 and 74 respectively) and obviously suffering from very advanced "osteochondrosis". Some of the author's statements are unacceptable, for instance, that disk herniation plays no part in the pathology of the cervical spine, that the L5 dermatome is situated at the lateral side of the foot, and that the reflex arc of the ankle-jerk involves L5 and S1, 2, and 3.] *F. K. Kessel.*

Synovectomy of the Knee Joint: A Review of the Literature and Presentation of Cases. PARDEE, M. L. (1948). *J. Bone Jt Surg.*, **30A**, 908.

This is a straightforward and unbiased account of the results of synovectomy and includes a full list of references on the subject. It should be read by those interested in the procedure. *G. E. Thomas.*

Some Anatomical Details of the Knee Joint. EAST, R. J. (1948). *J. Bone Jt Surg.*, **30B**, 683.

The deep and superficial parts of the medial ligament of the knee-joint are attached to the edge of the medial meniscus. The deep part of the lateral ligament (a part of the true capsule of the joint) is firmly attached by its posterior border—the arcuate ligament—to the edge of the lateral meniscus. The upper fibres of the popliteus muscle are inserted into this arcuate ligament and the lateral meniscus. The lateral meniscus is attached not only to the tibia by its cornua, but also to the femur by the strong ligaments of Humphry and Wrisberg. The movement of flexion takes place in the upper compartment of the joint because the menisci move with the tibia. Free rotation is possible only in the flexed position, because then the medial and lateral ligaments are relaxed and a smaller surface of the femur is in contact with the tibial plateau. It occurs in the lower compartment of the joint, the menisci moving with the femur. The posterior cruciate ligament forms the axis about which the tibia rotates and the movement is effected by the hamstring muscles. The popliteus has the important function of pulling the lateral meniscus posteriorly and out of the way of injury when medial rotation of the tibia occurs with the joint in the flexed position. The lateral rotation of the tibia which occurs when the position of the joint approaches full extension is affected by the lower fibres of the vastus lateralis. The popliteus is the antagonist. *H. Hughes.*

Intermittent Hydrarthrosis. (Nawracajaca puchlina stau ów kolanowych.) RUŻYŁŁO, E. (1948). *Polsk. Tyg. lek.*, **3**, 1110.

A case of this uncommon condition is reported in which the periodic recurrence of joint effusion affected one knee and then the other and later affected also the ankle-joints at regular intervals of 6 days. The effusions were at first painless; after 2 years the swelling was accompanied by tenderness, a rise of temperature, and an increase in erythrocyte sedimentation rate. Accepting allergic sensitivity as the cause of intermittent hydrarthrosis, the author concludes that there is only a quantitative difference between this syndrome and rheumatic disease of joints. *J. T. Leyberg.*

Lesions of Patellar Cartilage as a Cause of Internal Derangements of the Knee. PEABODY, C. W., and WALSH, F. P. (1948). *Arch. Surg. Chicago*, **57**, 589.

Lesions of the cartilage of the patella are second only to those of the menisci as a cause of internal derangement of the knee. They are of three types. (1) Congenital chondromalacia causes symptoms in the second and third decades which are usually mistaken for rheumatism. The whole of the cartilage is affected, lacking its normal hardness; it has a bluish tinge and an uneven, undulating surface. Areas of irregular fragmentation occur. (2) Traumatic chondritis follows a local tear. The surface elsewhere is at first normal; but since hyaline cartilage has no power of repair not only does the laceration persist, but it gradually enlarges from the trauma of continued friction and compression. (3) Degenerative chondrosis is a pre-senescent change found in patients over the age of 30. For many years it may be the only manifestation of such an arthrosis, progressing to affect the whole skeletal system. The cartilage is yellowish, with a granular surface and areas of fissuring and fragmentation.

The first type is treated by meticulous scalpel shaving of the entire articular surface of the patella down to the basal layer of cartilage. Localized currettage of the major defect only will not forestall the inevitable breakdown of the less involved areas. Patellectomy is contraindicated in the young age group for two reasons; first, there is a considerable capacity for repair of hyaline cartilage by fibrocartilage, and secondly, it is desirable to retain the protection afforded by the patella to the femoral condyles. The second type, when it is the result of patella fracture or recurrent dislocation of the patella, is best treated by patellectomy. In other circumstances the patella is retained for its protective function, and the treatment is a uniform shaving down of the entire involved facet to the level of deepest penetration of the traumatic defect. Patellectomy is the only satisfactory treatment for pre-senescent degenerative chondrosis. *H. J. Croot.*

Tenosynovitis of the Extensor Carpi Ulnaris Tendon Sheath. DICKSON, D. D., and LUCKEY, C. A. (1948). *J. Bone Jt Surg.*, **30A**, 903.

In this article 6 cases of non-suppurative tenosynovitis affecting the extensor policis brevis and the abductor longus policis are described.

Trauma is the usual predisposing cause, and pain—described as deep in the wrist-joint—the chief symptom. Examination reveals tenderness and swelling along the course of the tendon behind the lower end of the ulna

and clicking or grating may be felt over the affected part on moving the wrist. At operation in the 6 cases congestion and thickening of the synovial lining of the tendon sheath were found. The only reliable method of obtaining relief is by slitting the sheath ; although in some cases the thickened synovial lining was also removed, it is suggested that slitting alone is sufficient.

[Although the authors do not refer to the condition as a stenosing tenosynovitis it is clear from the description that some of the cases conform to this type of lesion.]

G. E. Thomas.

Hypertrophic Osteoarthropathy. TEMPLE, H. L., and JASPIN, G. (1948). *Amer. J. Roentgenol.*, **60**, 232.

The authors report 10 cases in all of which there were radiological changes of hypertrophic osteoarthropathy. Swelling of the joints and joint pains were the cause of 8 of these patients seeking advice, and radiological investigation of their joints revealed the periosteal proliferation in the neighbouring bones. In all 8 there were lung changes ; 6 were finally found to have a cancer of the lung, and the other 2 almost certainly had a malignant tumour of lung, though there was no positive pathological proof. Of the two patients who did not complain of joint pains and swelling but had hypertrophic osteoarthropathy, one had chronic myelogenous leukaemia whilst the other was suffering from non-tropical sprue.

These findings again show the importance of examination of the chest in such cases of hypertrophic osteoarthropathy. It is interesting to note that when the primary condition was removed there was rapid and complete disappearance of the symptoms arising from the hypertrophic changes. *L. G. Blair.*

Vertebral Osteomalacia. (" Osteomalacia " columnae.) THAYSEN, E. H. (1948). *Nord. Med.*, **39**, 1708.

Fifty cases of primary vertebral osteomalacia were treated at Bispebjerg Hospital between 1935 and 1946. The most common presenting symptom was pain, usually in the lumbar region but occasionally in the gluteal region or the thorax. Radiologically, the rarefaction of the vertebral bodies was very pronounced in every case and in 27 patients there was also a compression fracture of a lumbar and/or thoracic vertebral body. The serum calcium and serum phosphate levels were normal in every case, but in 24 cases the history suggested that the diet had been deficient in calcium or vitamin D. The patients were treated with a diet rich in calcium phosphate supplemented by a daily dose of 7,000 to 10,000 i.u. vitamin D_2. Follow-up examination of 30 patients in 1946 showed that only 23 had observed the dietary instructions given to them : in 21 of these there had been a subjective improvement in the form of decreased pain. Radiography revealed no sign of recalcification, but showed arrest of the disease. Of the 7 who had not continued treatment, 6 patients showed radiological signs of deterioration and 5 of these had pain. These therapeutic results suggest that the condition is a deficiency disease, but the preponderance of elderly women in the series seems to indicate that there may also be a hormonal factor at work. *B. Nordin.*

Boxer's Bursitis. WAXMAN, A., and GESHELM, H. (1948). *Calif. Med.*, **69**, 203.

Spalteholz describes the following bursae lying between the skin and the extensor tendons on the dorsum of the finger-joints : (1) dorsal digital subcutaneous bursae beneath the skin on the dorsal surface of the digital articulations ; (2) dorsal metacarpo-phalangeal bursae ; (3) intermetacarpo-phalangeal bursae over the dorsal aspect of the transverse capitular ligament, 1 to 3 in number. Among 523 injuries to professional and amateur boxers and wrestlers referred to in the present article there were 22 injuries to the knuckles of 21 boxers. Of these 22, 12 were simple contusions and were cured in a few days with hot soaks. The remaining 10—all in negroes—were diagnosed as traumatic bursitis of the affected knuckles, and this was confirmed by aspiration of bloody or gelatinous fluid. Of these 10 patients, 7 were cured by aspiration, hot soaks, strapping, and physical treatment, but in 3 operative removal of the bursa was necessary. *W. E. Tucker.*

The Treatment of Congenital (or Developmental) Coxa Vara. HORWITZ, T. (1948). *Surg. Gynec. Obstet.*, **87**, 71.

The results of a variety of surgical procedures used in the treatment of 17 cases of so-called congenital or developmental coxa vara are evaluated. Nothing new is brought to light.

Sciatica

A Study of " Surgical " Sciatica. Part played by Pseudomyxomatous Degeneration of Intervertebral Disk. Study of 59 Cases. (Contribution a l'étude des sciatiques chirurgicales. Place et rôle de la dégénérescence pseudomyxoïde du disque inter-vertébral. Statistique de 59 cas.) FONTAINE, R., DANY, A., and RIVEAUX, R. (1948). *Sem. Hôp. Paris*, **24**, 2415.

The authors report 59 patients with sciatica submitted to operation. They refuse to accept as a disk prolapse anything other than a clearly demonstrable protrusion of considerable size, and they found acceptable protrusions in only 20 of their 59 cases. Of the other patients, hypertrophy of the ligamentum flavum was accepted as the cause of the sciatica in 15, in 5 the pain was attributed to " bony lesions ", no fewer than 9 had neoplasms as the cause, 1 had an arachnoiditis, and no cause at all was found in 9.

The disk prolapses were more often (in 12 cases) situated in the space between the fourth and fifth lumbar vertebrae than in the lumbo-sacral space (8 cases). In all the 59 operations the lesion was exposed by a wide laminectomy of at least two vertebrae. Of the protruding masses of disk material, 9 were studied histologically. Five of these showed a pseudo-myxomatous degeneration, which the authors consider to be a very important cause of herniation of a disk. The degeneration does not affect nuclear material alone, but was seen quite well in the annular portion of the disk. It is considered that removal of the degenerate material is enough to cure the sciatica permanently. On the whole the results in the

prolapsed disk series were excellent. Over a prolonged follow-up period all the patients were found to be free from sciatica, and only 1 had any significant backache despite the very wide laminectomy.

Hypertrophy of the ligamentum flavum is held to be a not uncommon cause of sciatica. The cure rate after its appropriate treatment is, however, considerably lower than that after the removal of a prolapsed disk. Only 10 of the 15 cases of hypertrophy of the ligament gave good long-term results. The authors consider that undue importance is generally attached to disk herniation as a cause of sciatica and, quite apart from lesions of the ligamentum flavum, they state a case for consideration of lesions of intervertebral joints and other portions of the spine as possible causes. *D. Ll. Griffiths.*

Sciatica Caused by Cyst Formation in Old Hematoma : Report on Three Patients Treated Surgically. HERZ, R. (1948). *Surgery*, **24**, 714.

Three cases of sciatica successfully treated by the author by excision of a fibrous cyst in the region of the sciatic nerve are described. The patients were women (aged 46, 36, and 46 years) with a history of low backache, the pain radiating down the back of one thigh and leg and the history extending over many years. The onset was related to a fall or falls on the back. The pain was worse on sitting. There were areas of tenderness, usually over the lumbo-sacral spine and the sacro-iliac region on the affected side, and tender nodules, and " trigger areas " in the sacro-iliac region in which pain was relieved by local analgesia. In 2 of the cases a definite lump was palpable in the affected buttock. In the third case a lump was not palpable but the clinical picture so resembled that in the previous 2 cases that surgical exploration of the sciatic nerve in the buttock was undertaken and a fibrocystic mass found and excised. All 3 patients also had several fascial fat hernias.

Treatment consisted of surgical excision of the fascial fat hernias and of the fibrocystic mass. Microscopical examination of the latter showed fibrous cysts and fibro-adipose tissue, the seat of chronic inflammation. The lesions varied but were close to the sciatic nerve, so that with certain movements the nerve was subjected to abnormal pressure producing pain. The operation gave complete relief. *T. J. Evans.*

Sympathectomy in Sciatica. (Sympathectomi vid syndroma ischiadicum.) RÄSÄNEN, T. (1948). *Nord. Med.*, **40**, 1817.

Cases of sciatica where no disc herniation or other pathological cause of the typical pain has been discovered have generally been treated with " novocain " block of the lumbar sympathetic trunk ; the results have been good. If the blocks have given only temporary relief, lumbar sympathectomy has been resorted to in severe cases of sciatic pain, especially if the affected extremity is also cold and moist, which indicates alteration in the sympathetic reflex connexion. Sympathectomy was performed in 8 cases ; in 7 the result was good and in 1 there was no improvement. After the operation the temperature of the skin was normal. [Author's summary.]

Vascular Complication of Disc Surgery. HOLSCHER, E. C. (1948). *J. Bone Jt Surg.*, **30A**, 968.

During operative removal of a fourth lumbar disk the rongeur slipped right through the interspace and wounded a great vessel, but it was possible to complete the operation. It became clear later that an abdominal arterio-venous aneurysm had developed. After 6 months, laparotomy revealed a communication between the right common iliac artery and vein, each of which was ligated above and below the sac. Progress was satisfactory. [This is by no means the first of such accidents to be reported.] *David Le Vay.*

The Intraneural Topography of the Sciatic Nerve and its Popliteal Divisions in Man. SUNDERLAND, S., and RAY, L. J. (1948). *Brain*, **71**, 242.

The morphology of the sciatic nerve and its popliteal divisions was studied by dissection and serial section in material from 40 adult dissecting-room subjects. [This paper is so detailed and factual as to render a full summary impossible. Those interested should consult the original.] *R. Barer.*

Spinal Nerve Injury in Dorsolateral Protrusions of Lumbar Disks. LINDBLOM, K., and REXED, B. (1948). *J. Neurosurg.*, **5**, 413.

Intervertebral disk lesions are common. Among 160 patients between 14 and 87 years of age who died from various causes, 60 had nerve-root compression from disk or intervertebral joint lesions. In this paper 17 examples are discussed ; in only 6 of these had lumbago or sciatica occurred with certainty. Degenerative changes were found where the issuing nerve or its roots had been compressed, and especially in the ventral root fibres, and changes were noted in the posterior root ganglion, which in some cases was flattened. In these cases the ganglion as a whole showed an increased amount of connective tissue and gross alteration in its interior structure, the cells being often deformed and atrophied. The authors have investigated the question of the supposed association between arachnoidal proliferations and compressed roots, and found that such proliferations occur as frequently in relation to roots which have not been as in those which have been compressed. It seems to be wholly by chance that disk protrusions and arachnoidal proliferations sometimes affect the same segment.

[This demonstration of degenerative changes in the fibres of the roots and ganglion of the issuing spinal nerves as the result of compression by protruded nuclear material or enlarged intervertebral joints was to have been expected. Similar observations were made by Harvey Jackson in Britain in 1946.] *Lambert Rogers.*

Compression of the Cervical Spinal Cord by Herniated Intervertebral Discs. BUCY, P. C., HEIMBURGER, R. F., and OBERHILL, H. R. (1948). *J. Neurosurg.*, **5**, 471.

The authors deal with median herniations of cervical intervertebral disks producing cord symptoms. Details of 4 cases (all in men of middle age) are given. The authors stress that lumbar puncture should be performed

on every patient suspected to be suffering from a degenerative disease of the spinal cord, and that, if there is any suspicion that a herniated cervical intervertebral disk is present, myelography should be carried out with subsequent removal of the contrast medium. It is suggested that the symptoms may be caused by pressure on the anterior spinal artery, or projection of the cord backwards with consequent traction on the dentate ligaments, as postulated by Kahn. *Lambert Rogers.*

Headache : A Common Symptom of Cervical Disk Lesions. Report of Cases. RANEY, A. A., and RANEY, R. B. (1948). *Arch. Neurol. Psychiat., Chicago,* **59**, 603.

Headache due to pathological changes in the cervical disks may be located in the scalp, the face, or the cervical, suboccipital, or other region. If the orbital or temporal region is painful, the ipsilateral eye may be kept partly or completely closed. Movements in the cervical region may be limited, the patient maintaining his neck in a slightly tilted, rigidly fixed, or " poker neck " position. The muscles of the neck may be spastic, and with cervical scoliosis or lordosis unilateral prominence of the cervical muscles may be present. Of more importance are points of tenderness in the suboccipital and cervical regions, the pectoral girdle and the upper extremity.

When there is a cervical disk lesion some relief is usually afforded by maintaining head traction for a minute or so. This manoeuvre is not only of diagnostic value but also gives information about the probability of effective treatment by head traction. Loss of the normal cervical curve is the most consistent abnormality disclosed on *x*-ray examination. In most cases conservative treatment suffices ; few patients have such severe headache and associated radicular signs that operation is necessary. *R. M. Stewart.*

General Pathological Articles

The Clinical Value of the Antistreptolysin Reaction. An Account of the Results of the Reaction in 495 Patients. [In English.] AMLIE, R., and OEDING, P. (1948). *Acta med. scand.*, **131**, 288.

This is a record of the antistreptolysin reaction elicited by a modification of Kalbak's method in 495 so-called unselected patients. The results were unselected, but the sera were sent to the laboratory because the clinical picture suggested that the antistreptolysin titre might be significantly raised. The authors have accepted a titre figure up to 200 as being within possible normal limits, and have regarded only those titres above 200 as increased.

It is of interest to note in cases of acute polyarthritis, of which the antistreptolysin titre was increased in 80%, that the erythrocyte sedimentation rate may be falling rapidly while the antistreptolysin titre is still rising. Cases of primary chronic polyarthritis may have a normal antistreptolysin titre, but the secondary cases, especially when there are active signs, show an increased titre. [The definition of primary and secondary chronic polyarthritis is not apparent, although it is clear that acute polyarthritis signifies rheumatic fever.] Of 21 cases of acute nephritis 18, and all of 6 cases of acute tonsillitis, had an increased antistreptolysin titre. In general this increase was exhibited when the condition might be presumed to be associated with an acute *Streptococcus pyogenes* infection.

[In most of the cases recorded only one estimation was made. The advantages of serial estimations are obvious, especially in obscure conditions. This work suggests that the antistreptolysin titre is some indication of the activity of the disease, but until more extensive data have been collected the real value of the technique cannot be fully assessed.] *H. J. Bensted.*

Estrogens and Bone Formation in the Human Female. SHERMAN, M. S. (1948). *J. Bone Jt Surg.*, **30A**, 915.

A woman of 58 years, after panhysterectomy at the age of 34, developed severe deformities with bone pains and spontaneous fractures. Radiography disclosed a mixed picture of Paget's disease of a few, and severe decalcification of most, of her bones. Intensive oestrogen therapy caused rapid remission of her clinical symptoms with obvious improvement in the radiological picture, but later withdrawal of this therapy caused an exacerbation. After 2 years of treatment by daily doses of 0·33 to 1·66 mg. of oestradiol benzoate improvement had been maintained and no untoward symptoms had appeared.

[This is a very good article on the relation of oestrogens to bone formation and contains a full list of references.] *G. E. Thomas.*

Other General Articles

Reiter's Disease : A Study of 344 Cases Observed in Finland. [In English.] PARONEN, I. (1948). *Acta med. scand.*, Suppl. 212, 1.

This is a full report of the epidemic of Reiter's disease in Finland which was briefly described by Prof. Ö. Holsti at a recent Heberden Society meeting, and reported in the *Annals of the Rheumatic Diseases* of September 1948, Vol. 7, p. 180.

[On the basis of Dr. Paronen's material Reiter's disease would appear to be definitely associated with dysentery though this relation has not been clearly substantiated elsewhere. The low incidence of extragenital keratosis blennorrhagica is striking. The collection of the immense amount of data presented in this work, which also includes an extensive bibliography of 150 (mainly continental) references, is a very creditable achievement.] *R. R. Willcox.*

The Shoulder-Hand Syndrome in Reflex Dystrophy of the Upper Extremity. STEINBROCKER, O., SPITZER, N., and FRIEDMAN, H. H. (1948). *Ann. intern. Med.*, **29**, 22.

Forty-two cases of the shoulder-hand syndrome are reported, in 36 of which both the shoulder and the hand were involved. The aetiology in 11 cases could not be determined, 9 followed myocardial infarction, 5 trauma, and 5 a cerebrovascular accident. The

authors refer to a number of papers in the literature describing changes in the hand and/or shoulder following coronary infarction ; one reference occurs in Osler's *Principles and Practice of Medicine*, 1898 edition. Other conditions, such as osteo-arthritis of the cervical spine, hemiplegia, herpes, and nodular panniculitis, have also been described in the literature as being followed by symptoms in the shoulders and hands. The authors postulate the existence of a painful reflex arc of which (*a*) the afferent component is a sensory or autonomic nerve, (*b*) the component in the cord is the extensive network of interconnecting neurones described by Lorente de Nó as the internuncial pool, and (*c*) the efferent component is an autonomic and/or motor nerve. This hypothesis is considered to be the only one to account for the following features : (1) identical clinical pictures are produced by conditions differing widely in their location—for example, myocardial infarction, peripheral injuries, cerebral accidents ; (2) autonomic, motor, and sensory pathways are involved ; (3) the disturbance does not show a segmental distribution ; and (4) clinical improvement may follow sympathectomy. *H. A. Burt.*

Failure of Antireticular Cytotoxic Serum in Arthritis. KLING, D. H. (1948). *J. Lab. clin. Med.*, **33**, 1289.

The effect of Bogomoletz's antireticular cytotoxic serum (A.C.S.) in rheumatic conditions was investigated. It is concluded that there is no indication for A.C.S. in the treatment of osteo-arthritis and fibrositis. In rheumatoid arthritis and spondylitis, conditions which are resistant to other treatment, a trial may be justified. *J. Koszyk.*

New Pharmacological Features of Salicylates. (Nuevos aspectos farmacológicos del salicilato.) CÉSARMAN Y VITIS, T. E., and MARTIN, S. (1948). *Arch. Inst. Cardiol. Méx.*, **18**, 373.

A rapid and simple method of determining the serum salicylate level is described and shown to be comparable with the method used by Coburn. The administration of sodium salicylate and acetylsalicylic acid in doses of 0·1 g. per kilo every 24 hours produced a rapid elevation of the serum level to between 332 and 561 g. per 100 ml. if given in divided doses at 12-hour intervals. If given 2-, 3-, 6-, or 8-hourly, lower serum levels were obtained. *W. T. Cooke.*

The Antirheumatic Effect of Sodium Gentisate. MEYER, K., and RAGAN, C. (1948). *Science*, **108**, 281.

The authors conclude that sodium gentisate appears to be equal to, or more effective than, salicylate in rheumatic conditions, and that the action of salicylates is probably due to its oxidation product gentisate.

Titles of the Articles in the Current Literature

Pathogenesis of Rheumatic Fever. KERR, W. J. (1948). *Ann. intern. Med.*, **29**, 587.

Diagnostic Aids in Rheumatic Fever. CONNOR, C. A. R. (1948). *J. Mich. med. Soc.*, **47**, 1339.

A Community Program for the Control of Rheumatic Fever. GRIFFITH, G. C. (1949). *Amer. J. publ. Hlth.*, **39**, 61.

The Electrocardiogram in Rheumatic Fever. KAHN, J., SHAPIRO, E., and LIPKIS, M. L. (1948). *Calif. Med.*, **69**, 449.

Occurrence of the Wolff-Parkinson-White Syndrome Concomitant with Acute Rheumatic Fever. MENEELY, J. K. (1948). *Yale J. Biol. Med.*, **21**, 87.

Epidemiology of Rheumatic Fever and Some of its Public Health Aspects. FORTUNE, C. (1949). *Med. J. Aust.*, **1**, 373.

Some Clinical Aspects of Rheumatic Fever. MADDOX, K. (1949). *Med. J. Aust.*, **1**, 375.

Specific Rheumatism. Some Cases of Atypical Rheumatic Fever. (Rheumatismus specificus. Nogle Tilfaelde af atypisk Febris Rheumatica.) REITER, H. F. H. (1948). *Maandskr. prakt. Laegegern.*, **26**, 405.

Monosymptomatic Form of Acute Rheumatism. (Forme mono-symptomatique de la maladie de bouillaud.) BENMUSSA, —. (1949). *Tunisie med.*, **37**, 29.

Atypical Visceral Form of Acute Rheumatism. (Forme atypique vescerale de la maladie de bouillaud.) BENMUSSA, —., CARUANA, —., DIDIER, —., and GALES, —. (1949). *Tunisie med.*, **37**, 35.

Clinical Observations on Treatment of Acute Rheumatism with Sodium Salicylate and Aspirin. (Observations cliniques concernant le traitement de la maladie de bouillaud par le salicylate de soude et l'acide acétylsalicylique.) ROSKAM, J. (1948). *Acta clin. belg.*, **3**, 305.

Results to be Expected from Intra-arterial Injection of Streptococcus-enterococcus Anavaccine in the Treatment of Prolonged Forms of Acute Rheumatism. (Ce que l'on peut attendre des injections intra-artérielles d'un ana-vaccin strepto-entérococcique dans le traitement des formes traînantes de la maladie de Bouillaud.) DEBRAY, M., and PROVENDIER, M. (1949). *Sem. Hôp. Paris*, **25**, 975.

Rheumatic Fever in Childhood. KISS, P. (1949). *Paediat. danub.*, **4**, 291.

Oxidative Processes in Acute Rheumatism in Childhood. [In Russian.] POROIKO, V. A., and RABINOVICH, A. L. (1948). *Pediatriya*, **4**, 23.

Acute Rheumatism in Children in War and in the Post-war Period and its Connexion with Scarlet Fever. [In Russian.] LEVIN, E. R., and LEVINA, S. M. (1948). *Pediatriya*, **4**, 18.

Monocytic Reactions in Different Forms of Rheumatism in Childhood. [In Russian.] GRIGOROVA, O. P. (1948). *Pediatriya*, **4**, 32.

Salicylate Medication in the Treatment of Rheumatic Diseases of Children. Study of Salicylate Levels in Blood. (La medicación salicilada en el tratamiento de las enfermedades reumaticás del niño. Estudio de los niveles salicilémicos.) GORREA, B. D. (1948). *Bol. liga urug. Reum.*, **2**, 134.

Changes in Plasma Protein in Rheumatism in Childhood. (Die Bluteiweisskörperveränderungen bei der rheumatischen krankheit im Kindesalter.) SCHWARZ-TIENE, E. (1948). *Ann. paediatr., Basel*, **171**, 381.

Chronic Juvenile Rheumatoid Arthritis (Still's syndrome). (Chronické reumatoidni arthritidy mladistvých (Stillův syndrom).) RINGEL, J., and JANELE, J. (1949). *Lek. Listy*, **4**, 169.

Medico-social Study of Juvenile Rheumatism. Statistical Data on 310 Cases. (Estudio medicosocial del reumatismo infantil. Datos estadísticos sobre 310 fichas.) REY SUMAY, R. S. (1948). *Rev. argent. Reum.*, **13**, 193.

Sulphonamide Prophylaxis in Convalescent Rheumatism. A Preliminary Report. DE GRESPIGNY, G. (1948). *Clin. Rep. Adelaide Child. Hosp.*, **1**, 139.

Clinical Features of Rheumatoid Arthritis. (Aspectos clinicos de la artritis reumatoidea.) ARMAS CRUZ, R., MEREDITH, J. C., VALENZUELA, F., and LACKINGTON, C. (1948). *Rev. méd. Chile*, **76**, 625.

Rheumatoid Arthritis. The Importance of a Comprehensive Approach in Treatment. BAUER, W. (1948). *J. Amer. med. Ass.*, **138**, 397.

The Modern Treatment of Rheumatoid Arthritis. BAYLES, T. B. (1948). *Med. Clin. N. Amer.*, **32**, 1357.

The Basic Treatment of Rheumatoid Arthritis. WEISS, T. E. (1949). *N. Orleans med. Surg. J.*, **101**, 496.

Colchicum in the Treatment of Acute and Chronic Rheumatism not of Gouty Origin. (Il colchico nella terapia dei reumatismi acuti e cronici non gottosi.) LUCHERINI, T. (1948). *Progr. med., Napoli*, **5**, 524.

Undecylenic Acid by Mouth in the Treatment of Arthritis and Bursitis. A Preliminary Report. PERLMAN, H. H. (1949). *Urol. cutan. Rev.*, **53**, 103.

Sulphonamide Therapy in Rheumatoid Arthritis. PARR, L. J. A., and SHIPTON, E. (1949). *Rheumatism*, **5**, 25.

Present Status of Gold Therapy in Rheumatoid Arthritis. WRIGHT, H. P. (1948). *Canad. med. Ass. J.*, **59**, 359.

Rheumatoid Arthritis. 475 Cases Treated with 721 Courses of Gold. COHEN, A., DUBBS, A. W., and GOLDMAN, J. (1948). *Penn. med. J.*, **52**, 35.

Therapy of Rheumatoid Arthritis with Gold. (Leceni chronickeho kloubniho reumatismu zlatem.) NOVOTNY, K. (1948). *Publ. Fac. Méd. Brno*, **21**, 133.

Personal Studies on the Treatment of Rheumatoid Arthritis with Gold Salts. (Contribution personnelle á l'étude du traitement de l'arthrite rhumatismale par les sels d'or.) MANTHA, L. (1949). *Un. méd. Can.*, **78**, 35.

The Dosage of Gold in Rheumatoid Arthritis. (De dosering van goud bij chronisch gewrichtsrheuma.) KUIPERS, R. D. W. (1949). *Ned. Tijdschr. Geneesk.*, **93**, 1240.

Observations on Gold Therapy of Rheumatoid Arthritis. (Observaciones sobre la auroterapia de la artritis reumatoidea.) CRUZ, R. A., MEREDITH, J. C., VALENZUELA RACEST, F., and LACKINGTON, C. (1948). *Rev. med. Chile*, **76**, 765.

Pulmonary Complication Following Use of Gold Salts. Report of a Case Treated by BAL. [In English.] SAVILAHTI, M. (1948). *Ann. Med. intern. fenn.*, **37**, 263.

The Role of Allergy in Rheumatoid Arthritis and a Suggested Treatment. Preliminary Report. ROCKWELL, G. E. (1949). *Ann. Allergy*, **7**, 195.

Rheumatoid Arthritis—Food Allergy as a Factor. ZELLER, M. (1949). *Ann. Allergy*, **7**, 200, 239.

Flat Foot in Rheumatoid Arthritis. (Il piede piatto nell' artrite reumatoide.) CECCHI, E. (1948). *Progr. med., Napoli*, **5**, 528.

Management of the Rheumatoid Arthritic Patient by the Physiotherapist. BURT, H. A. (1949). *Physiotherapy*, **35**, 3.

Physical Treatment in the Rheumatic Diseases and in some Other Painful Conditions. BURT, H. A. (1948). *Brit. J. phys. Med.*, **2**, 173.

Occupational Therapy in Articular Rheumatism. LIGHT, S. (1949). *Rheumatism*, **5**, 48.

Pathogenesis of Neutrophil Leucopenia in Rheumatoid Arthritis with Hepatomegaly and Splenomegaly (Felty Syndrome). (Pathogenesis der neutrophiele leucopenie in rheumatoiede arthritis met hepato-splenomegalie (Syndroom van Felty). VANDENBROUCKE, J. and VANDEPUTTE, M. (1948). *Verhandelingen*, **10**, 390.

Conditions Simulating Rheumatoid Arthritis. FAHRNI, B. M. (1948). *Bull. Vancouver med. Ass.*, **25**, 23.

Surgery in the Treatment of Chronic Arthritis. KELIKIAN, H. (1949). *Surg. Clin. N. Amer.*, **29**, 87.

Chronic Rheumatism and Pseudo-rheumatic Arthropathies in Diseases of the Nervous System. (Rhumatismes chroniques et arthropathies pseudorhumatismales au cours des maladies du système nerveux.) RAVAULT, P. P., THIERS, H., and BERTHIER, L. (1949). *Rev. Rhum.*, **16**, 1.

Dental Sepsis and Chronic Rheumatism. KERSLEY, G. D. (1949). *Proc. R. Soc. Med.*, **42**, 151.

Chronic Inflammatory Rheumatism and Focal Infection. Experience in 136 Cases of Rheumatoid Arthritis and in 53 Cases of Rheumatism Associated with a Septic Focus. (Reumatismos cronicos inflamatorios e infección focal. Experiencia en 136 casos de artritis reumatoides y en 53 casos de reumatismos septicos focales.) LOSADA, M., and FRANCE, O. (1949). *Rev. argent. Reum.*, **13**, 207, 219, 254, 274.

Chronic Forms of Rheumatism. General Considerations and Notes on Nomenclature and Classification. (Reumatismos cronicos, consideraciones generales y anotaciones sobre nomenclatura y clasificacion.) CRUZ, R. A., MEREDITH, J. C., LACKINGTON, C., and RAVEST, F. V. (1948). *Rev. med. Chile*, **76**, 559.

Treatment of Chronic Infective Rheumatism by Congo Red. (Tratamiento de los reumatismos infecciosos tórpidos con rojo Congo.) JIMÉNEZ DÍAZ, C., LÓPEZ GARCÍA, E., and CENTENERA, D. (1948). *Rev. clin. esp.* **30**, 365.

The Treatment of the Locomotor Disorders by Electrophoresis of Sulphur Compounds (Mozgásszervi betegségek gyógyítása kénvegyületek elektrophoresisével.) PETRÁNYI, G., and RIESZ, E. (1948). *Orv. Lapja*, **4**, 1208.

The Clinical Response to Vaccine in 125 Cases of Rheumatic Disease. PHILLIPS, K. (1949). *Rheumatism*, **5**, 53.

The Role of Hormones in Growth and Ageing of the Skeleton and their Significance in the Pathogenesis of Arthritis Deformans. (Die Rolle der Hormone im Wachstum und Altern des Skeletts und ihre Bedeutung für die Pathogenese der Arthritis deformans.) SILBERBERG, M., and SILBERBERG, R. (1949). *Schweiz. med. Wschr.*, **79**, 127.

Generalized Dormal Infiltration During Rheumatism. (Infiltración dérmica generalizada en el curso de la enfermedad reumática.) PISANO, A. (1948). *Bol. Liga urug. Reum.*, **2**, 125.

Intracutaneous Serum Injections in the Treatment of Rheumatic Disorders. (Die intrakutane Serumbehandlung rheumatischer Erkrankungen.) HEINSEN, H. A. (1947). *Dtsch. GesundhWes.*, **2**, 401.

Sex-hormone Implantation in the Treatment of Rheumatic Conditions. WEIL, M., and SICHERE, R. M. (1948). *Rheumatism*, **4**, 224.

Use of Intracaine in Oil for the Relief of Pain Involving the Musculo-Skeletal System. LEVEY, P. (1948). *Rheumatism*, **4**, 234.

Effects of Temperature and Ultraviolet Light on Experimental Polyarthritis of Rats. TRIPI, H. B., GARDNER, G. M., and KUZELL, W. C. (1949). *Proc. Soc. exp. Biol., N.Y.*, **70**, 45.

Comments on Focal Mono-arthritis. (Comentarios sobre las monoartritis focales.) CUATRECASAS, J. (1948). *Rev. argent. Reum.*, **13**, 114.

Prevention of Deformity in Chronic Polyarticular Rheumatism. (Sulla prevenzione delle deformitá nei reumatismi poli-articolari cronici.) ROSSI, A. (1949). *Minerva med., Torino*, **1**, 205.

Simultaneous Development of a Chronic Progressive Polyarthritis and an Extrapyramidal Syndrome. (Evolution simultanée d'une polyarthrite chronique évolutive et d'un syndrome extrapyramidal.) EUZIÈRE, J., PAGES, P., LAFON, R., MIROUZE, J., and SALVAING, J. (1949). *Rev. Rhum.*, **16**, 26.

Reactions of the Cerebrospinal Fluid During Chronic Polyarthritis. (Les reactions du liquide céphalo-rachidien au cours des polyarthrites chroniques.) GRABER-DUVERNAY, J., and GERBAY, F. (1949). *Rev. Rhum.*, **16**, 24.

Can Polyarthritis Rheumatica be Induced by Trauma ? (Kan reumatisk polyartrit utlösas av trauma ?) JONSSON, E., and BERGLUND, K. (1949). *Nord. Med.*, **41**, 7.

The Treatment of Chronic Polyarthritis with Copper Salts. (Chronicus polyarthritisek kezelése réz-sókkal.) DIVÉNYI, A. (1948). *Orv. Lapja*, **4**, 1210.

Experimental and Clinical Study of the Action of Sand Baths on the Normal and the Polyarthritic Subject. (Etude expérimentale et clinique sur l'action du bain de sable sur le sujet normal et le polyarthritique.) HEUSCHEROISLER, R. (1948). *Rev. med. Suisse rom.*, **68**, 638.

Observations on Periarthritis of the Shoulder and its Treatment. (Observaciones sobre periartritis del hombro y su tratamiento.) GAUDIANO, P. (1948). *Bol. Liga urug. Reum.*, **2**, 117.

Practice and Results of Osteopathy. (La pratique et les resultats du travail osteopathique.) DOUGLAS, W. (1948). *Rev. Rhum.*, **15**, 351.

Stenosing Vaginitis and Recto-sigmoiditis due to Lymphogranuloma Venereum with Multiple Osteo-arthropathic Complications. (Vaginite e rettosigmoidite stenosanti linfogranulomatose (Nicolas-Favre) con complicanze osteo-artropatiche multiple.) MIDANA, A. (1949). *Minerva med., Torino*, **1**, 206.

Arthroses of the Elbow due to Minimal Trauma. (Les " arthroses " microtraumatiques du coude.) RUELLE, M. (1949). *Rev. Rhum.*, **16**, 49.

Acid Injections in the Treatment of Painful Osteoarthritis. BOSC, F. V. A. (1948). *Med. Pr.*, **220**, 563.

Ankylosing Spondylitis with Peripheral Arthritis. COX, A. G. (1948). *Guy's Hosp. Rep.*, **97**, 124.

Radiological Observations on Spondylitis Deformans as a Manifestation of Rheumatism. (Commenti radiologici sulle spondilosi deformanti nel quadro delle malattie reumatiche.) DE BERNARDI, E. (1948). *Ann. Radiol. diagnost.*, **20**, 349.

Morquio's Syndrome. (Les chondrodysplasies spondyloepiphysaires congenitales (Syndrome de Morquio).) LAYANI, F., and DURUPT, L. (1948). *Rev. Rhum.*, **15**, 305.

Interview Therapy of Psychosomatic Arthritis. LAW, S. G. (1949). *Rheumatism*, **5**, 38.

Psychosis due to Chronic Rheumatism. (Intorno alla psicosi reumatica cronica.) LUZZATTO, A. (1948). *Rass. Studi psichiat.*, **37**, 525.

The Index of Haptoglobin in Blood in Rheumatic Affections. (L'indice d'haptoglobinémie dans les affections rhumatismales.) COSTE, F., JAYLE, M.-F., and DELBARRE, F. (1948). *Bull. Soc. med. Hop. Paris*, **4**, 1221.

Trigger-points of Shoulder-girdle Muscles in Arm Pain. (Les " trigger-points " des muscles de la ceinture scapulaire dans les brachialgies.) VEREECKEN, E. (1949). *Rev. Rhum.*, **16**, 60.

Fibrositis in the Muscles of Mastication. (With Reference to the Masseter Muscle.) SNAWDON, J. W. E. (1949). *Proc. R. Soc. Med.*, **42**, 153.

The Treatment of Chronic Rheumatism (Especially " Fibrositis ") by the Use of Adrenalin Cream. MOSS, L. (1949). *Med. World, Lond.*, **70**, 244.

Sleep Posture : Costo-Vertebral Manipulations. MCDONNELL, J. (1948). *Rheumatism*, **4**, 239.

Incomplete Transverse Division of the Fifth Lumbar Vertebra. (Bipartition transversale incomplete de la cinquieme vertebre lombaire.) RUBENS-DUVAL, A., and BELLIN, A. (1948). *Rev. Rhum.*, **15**, 245.

Latent Involvement of the Sacro-iliac Joints in Prolonged Gonococcal Infection. (L'atteinte latente des sacro-iliaques au cours de l'infection gonococcique prolongee.) THIERS, H. (1948). *Rev. Rhum.*, **15**, 219.

Two Cases of Syphilis of Bone. (Deux case de syphilis osseuse.) LIÈVRE, J.-A., BLOCH-MICHEL, H., and SOLIGNAC, H. (1948). *Rev. Rhum.*, **15**, 244.

Static Causes of Vertebral Pain. (A propos des algies vertébrales d'origine statique.) DELCHEF, J., and WALCH, A. (1948). *Rev. Rhum.*, **15**, 165.

Two, Apparently Primary, Cases of Ivory Vertebrae. (Due casi di vertebra eburnea apparentemente primitiva.) LISCHI, G. (1948). *Radiolog. med., Torino*, **34**, 385.

The Position of Rest of the Spine in the Treatment of Sciatica, Malum Coxae, Frozen Shoulder. FARKAS, A. (1949). *Rheumatism*, **5**, 7.

Low Backache Due to Changes of the Intervertebral Disks. (A porckorongok elváltozásai okozta derék-táji fájdalmak.) LISZAUER, D. (1948). *Orv. Lapja*, **4**, 1349.

High Cervical (Invobrine Occiput Atlas, Axis and 3rd Cervical Vertebra). Diagnostic Error. (Espondilitis cervical alta occipito-atloidea-tercera cervical. Grave error del diagnóstico.) COSTA BERTANI, G. (1948). *Rev. argent. Reum.*, **13**, 1189.

Traction Carried Out on a Table for Therapy of Vertebral Affections. Indications and Results. (Les tractions sur table de vertébrothérapie. Premières impressions sur les indications et sur les résultats de la méthode.) DE SÈZE, S., and LEVERNIEUX, J. (1949). *Pr. méd.*, **57**, 28.

Gout Simulating Rheumatoid Arthritis. READ, W. A., and BUXTON, R. (1948). *Va med. Mon.*, **75**, 493.

Pathological Physiology of Uric Acid : Diagnosis and Treatment of Gout. (Fisiología patológica del ácido úrico : Diagnóstico y tratamiento de la gota.) DELGADO, E., and DELGADO, —. (1949). *Clin. y Lab.*, **47**, 93.

Treatment of Dupuytren's Contracture. (La thérapeutique de la maladie de Dupuytren.) CORNIL, M. (1949). *Rev. Rhum.*, **16**, 58.

Bladder Neck Disease and Rheumatism. HOCK, E. (1949). *Urol. cutan. Rev.*, **53**, **149**.

Obstacles to a Rational Nomenclature for Rheumatism. (Obstáculos a una racionalización de la nomenclatura reumatológica.) TARNOPOLSKY, S. (1948). *Rev. Asoc. med. argent.*, **62**, 597.

Dietetics in Rheumatism. (La dietetica en los reumatismos.) KLEIMANS, M. (1949). *Rev. argent. Reum.*, **13**, 224.

The Social Importance of Rheumatic Diseases in Sweden. [In English.] BOHMAN, F. (1948). *Acta med. scand.*, **132**, 150.

Social and Economic Aspects of the Rheumatic Diseases. Mackintosh, J. M., and KNOWELDEN, J. (1948). *Brit. J. phys. Med.*, **2**, 177.

The Diagnosis and Treatment of Gout. SACASA, C. F. (1948). *Ann. w, Med. Surg.*, **2**, 307.

Gout: Report of an Unusual Case in a Young Man. BERK, M. E. (1948). *Amer. J. med. Sci.*, **215**, 290.

Some of the Problems in the Education of Rheumatic Children. LEVITT, J., and TARAN, L. M. (1948). *J. Pediat.*, 9, **32**, 553.

Medical Hydrology and the Four Causal Factors in Rheumatic Diseases. VAN BREEMEN, J. (1948). *Arch. med. Hydrol., London.*, **18**, 3.

Treatment with Bacterial Filtrates. BARFORD, L. J. (1948). *Rheumatism*, **4**, 214.

The Problem of Rheumatism. DOUTHWAITE, A. H. (1948). *Practitioner*, **161**, 153.

Some Industrial Aspects of Rheumatism. FERGUSON, T. (1948). *Practitioner*, **161**, 170.

Luxating Arthropathies of the Lower Limbs. (Arthropathies disloquantes des membres inférieurs.) LIÈVRE, J. -A. (1948). *Rev. Rhum.*, **15**, 144.

Trochanteric Metastasis of Neoplasm Simulating Arthrosis of Hip. (Métastase néoplasique trochantérienne simulant une coxarthrose.) FORESTIER, J. (1948). *Rev. Rhum.*, **15**, 142.

Hypertrophic Osteoarthropathy during the Course of a Haemorrhagic Recto-colitis. (Ostéoarthropathie hypertrophiante pneumique au cours d'une recto-colite hémorragique.) COSTE, F., GALMICHE, P., and SORS, C. (1948). *Rev. Rhum.*, **15**, 140.

Spa Treatment of Rheumatic Neuralgias. (Tratamiento hidromineral de la neuralgias reumáticas.) VALENZUELA, D. M. A. (1948). *Farm. Terap.*, **1**, 69.

Scheuermann's Disease. (La maladie de Scheuermann.) BROCHER, J. E. W. (1948). *Rev. Rhum.*, **15**, 181.

The Modern Classification of Diseases of the Locomotor System, Commonly Called Rheumatism. (A rheuma gyüjtónev alá tartozó mozgásszervi betegségek új felosztása.) RIESZ, E. (1948). *Orv. Lapja*, **4**, 1152.

On the Nature of Rheumatism. (Sur la nature du rhumatisme.) PEMBERTON, R. (1948). *Un méd. Can.*, **77**, 1056.

Origin of Rheumatic Diseases. (Ueber die Entstehung der rheumatischen Krankheiten.) WINBLAD, S. (1948). *Schweiz. med. Wschr.*, **78**, 684.

The Management of the Rheumatic Patient. BACH, F. (1948). *Physiotherapy*, **34**, 147.

Unusual Forms of Rheumatic Pain. CECIL, R. L. (1948). *J. Mich. med. Soc.*, **47**, 516.

Standards for the Diagnosis of Activity in the Rheumatic State. ROSENBLUM, H. (1948). *Calif. Med.*, **69**, 25

THE HEBERDEN SOCIETY

SUMMARY OF CASE CONFERENCE HELD AT THE WEST LONDON HOSPITAL ON FRIDAY, APRIL 8, 1949

A meeting of the Heberden Society was held at the West London Hospital on April 8, 1949. This was in the form of a Case Conference, using the technique developed by the School of Social Medicine at Oxford, and applied experimentally to the problem of the rheumatic diseases. The Case Conference technique is an attempt to approach medicine from the clinico-social rather than the clinico-pathological standpoint.

The Chair was taken (at the invitation of the President, Dr. W. S. C. Copeman) by Dr. Alice Stewart, Assistant Director of the School of Social Medicine at Oxford. Dr. Copeman opened the meeting by drawing attention to the suggestion that the teaching hospitals had diverted their attention from the social aspects of diseases by their concentration on the pathological approach and by their necessity to produce so-called good teaching material.

Two cases were presented by Dr. R. M. Mason : one a case of early rheumatoid arthritis in a young woman, with considerable remission and a good functional result, and the other a case of severe ankylosing spondylitis in a young man, with ankylosis of both hip joints and involvement of the spine and peripheral joints, on whom a bilateral cup arthroplasty of the hip joints had been carried out, but there remained very serious functional incapacity.

Miss M. W. Edminson, Head Almoner of the Arthur Stanley Institute, Middlesex Hospital, and Miss B. E. Leman, Out-patient Almoner, West London Hospital, gave a full account of the social work carried out by their departments.

Opening the discussion Dr. Stewart questioned whether these cases would have occurred at all if social research work had been carried out as actively as had pathological. This was due, she suggested, to reluctance to use a statistical approach to such problems, which involves isolating the community and then applying a proper epidemiological study to it. She thought that such a method could be applied to the rheumatic diseases and that special departments should be set up to study the problem.

She criticized the technique of presentation, saying that the meeting had heard details of the work done in collecting the social information, at length, but that there was no fundamental architecture to the social side of case-taking at present. She suggested various headings under which specific information was required, including the family constitution, an assessment of major financial stresses, the housing arrangements, the relevant public services available, the follow-up arrangements, and the final assessment of results.

In discussion the problems of population studies were discussed. Dr. Heald suggested that numerical values should be given empirically to the various factors mentioned by Dr. Stewart so that the physician in charge of a case could make a rapid assessment of the significance of the relevant social factors. Such figures, he thought, might also be of statistical value. Miss Edminson said that, though the statistical information which could be obtained from their work was important, it was the individual service of the almoner to the patient which should have priority.

Dr. Stewart put forward the suggestion that a committee of interested doctors and almoners should be set up to work out the main headings to be used in a social case report which would enable definite information to be obtained.

VISIT TO OXFORD ; JULY 15 AND 16, 1949

The Heberden Round for 1949 was held at the Radcliffe Infirmary, Oxford, on July 16. In the absence of Professor L. J. Witts, Dr. Sidney Truelove, First Assistant to Professor Witts, took the Round ; the President, Dr. W. S. C. Copeman, and thirty-nine members and guests, attended. The Round was in the form of a demonstration for discussion of seven cases in the Maternity Lecture Theatre of the Hospital. Members were welcomed by the Regius Professor of Physick, Prof. A. D. Gardner.

Case 1 : presented by Dr. Truelove.—A girl of 28 years, with sclerodactyly, beginning with a polyarthritis with subsequent Raynaud syndrome of the hands, was treated with cervical sympathectomy but this did not give any relief, and there was subsequent obliteration of the radial pulse on the side treated. Later a scleroderma of the face and hands developed, followed by dysphagia. This was found to be due to scleroderma of the oesophagus, and partial oesophagectomy had been carried out with satisfactory results. Dr. Robb-Smith showed slides of the specimen obtained at operation.

Case 2 : presented by Dr. Reader.—This was a case of rheumatoid arthritis and Sjogren's syndrome in a woman of 29 with symptoms of swellings of her parotid glands and dryness of the mouth, beginning nine years previously. There was also soreness of the eyes, and tests for kerato-conjunctivitis sicca were positive. Seven years after the onset of these symptoms rheumatoid arthritis developed. There was also persistent protein urea, and an intravenous pyelogram showed unusual punctate calcification in the renal pyramids. All renal function tests were, however, normal.

Dr. Pugh described similar cases and suggested methods of testing her salivary secretion quantitatively. He also pointed out the widespread nature of the condition, involving bronchial as well as gastro-intestinal secretion.

Case 3 : presented by Dr. Zinovieff.—Neuritis of the deep branch of the ulnar nerve, presumably traumatic and occupational in origin, occurred in a man of 50 who

showed well marked wasting of the first two interosseous spaces and of the abductor pollicis without sensory changes.

Case 4 : presented by Dr. White.—Spondylitis and rheumatoid arthritis occurred in a farm-worker aged 49, whose symptoms began many years before, with acute onset in the lumbar region and with some remission subsequently. During the past three years his symptoms had become severe and progressive, spreading from the lumbar region to the neck, involving the jaw, knees, shoulders, elbows, wrists, and fingers. He had been treated with deep *x*-ray, since changes suggestive of ankylosing spondylitis were apparent on radiographic examination of the sacro-iliac joints. Subsequently the erythrocyte sedimentation rate, which had been moderately raised only, became elevated. He became anaemic, and the albumin-globulin ratio was reversed. He had also developed a gastric ulcer ; he had been treated with intensive salicylate therapy, and the sedimentation rate had rapidly fallen to its previous level of around 30 mm. in the first hour.

Discussion followed. The relationship between ankylosing spondylitis and rheumatoid arthritis, and the divergence between British and American views, was considered. The conclusion reached was that this was probably a case of true ankylosing spondylitis involving the peripheral joints as well.

Case 5 : presented by Dr. Walsh.—A taxi-driver aged 39 who developed pain, swelling and stiffness, of the ankles and knees two years previously, and who was found to have clubbing of the fingers and toes, was considered as a result of a chest radiograph to have carcinoma of the lungs, which showed generalized increased markings and which had been treated with nitrogen mustard. His subsequent improvement was such that the diagnosis of carcinoma had been abandoned. Numerous other diagnoses had been made. Dr. Walsh suggested that he had pachyderma with pachyperiostitis.

A general discussion on the aetiology of clubbing followed, including the anoxic, lymphatic block, and increased peripheral blood flow hypotheses.

Case 6 : presented by Dr. Watts.—This was a case of idiopathic steatorrhoea in a girl of 18, whose first symptoms were anaemia and osteomalacia. The original diagnosis had been that of aplastic anaemia, and she had been treated with blood transfusions. The diagnosis became apparent when shortening of one leg was noted. A radiograph showed a spontaneous fracture of the femur with osteomalacia. Further investigation showed the presence of steatorrhoea. After further treatment, her condition had become extremely good, her main disability arising from the shortening due to her old fracture.

Case 7 : presented by Dr. Reynell.—This was a case of chronic hepatitis in a mental nurse aged 49, following an attack of infective hepatitis in 1940. Within three years there was markedly abnormal liver function with gross oedema and ascites which required frequent tapping. Omentopexy was carried out in 1945 and subsequent improvement was marked ; within two years the ascites had disappeared, although she had a subsequent attack of jaundice. Her condition is now such that she is able to work.

NEW YORK RHEUMATISM ASSOCIATION

The Annual Meeting of the New York Rheumatism Association took place on April 23, 1949, at the Cornell University Medical College. Dr. Otto Steinbrocker, New York, presided.

The first paper presented was on the sheep cell agglutination test for rheumatoid arthritis by Robert Brown, Charles Illes, Joseph J. Bunim, and Currier McEwen. A suspension of sheep red blood cells was sensitized with rabbit serum. Serial dilutions were made and a fixed amount of the serum of patients with rheumatoid arthritis was added to the tubes and incubated. The test was performed in the manner described by Rose and others. A series of 177 patients with rheumatoid arthritis was tested. Eighty-two with other diseases and normals served as a control. A positive differential titre is one to sixteen or greater. There was only one false positive. Of sixty-two patients tested who had active rheumatoid arthritis, 55 per cent. gave positive reactions. In patients with inactive disease, 29 per cent. had a positive test. Nine cases of rheumatoid spondylitis had a negative reaction. A close but not exact correlation was found between the sheep cell agglutination test and the haemolytic streptococcus agglutination test.

Otto C. Kestler presented the paper on histopathology of the intrinsic muscles of the hand in rheumatoid arthritis which had appeared in the *Annals of the Rheumatic Diseases* for March, 1949, vol. 8, p. 42.

The last paper was on chemical analysis of fresh skeletal muscle of patients with various rheumatic diseases by Edward J. Bien, Morris Ziff, Joseph J. Bunim, and Currier McEwen. Muscle removed by biopsy in patients with various rheumatic and non-rheumatic diseases was chemically analysed for its content of total protein, myosin, collagen, water, and adenosine triphosphate activity. It was found that the total protein content decreased with atrophy. This decrease of total protein was not diagnostic of any particular disease, but was quite evident in osteo-arthritis and gout. Surprisingly, the collagen content of muscle remained constant regardless of the disease or degree of atrophy of muscle. Myosin content of muscle was found to fall in diseases without atrophy, but greater falls were noted where atrophy was present. The fall of muscle myosin was not specific of any disease. Adenosine triphosphatase activity was found to be independent of the myosin content. The activity was found to be decreased in rheumatic diseases without atrophy and still further decreased in diseases with muscle atrophy. Atrophy of muscle was associated with a decreased water content, presumably due to replacement by fatty tissue.

At a meeting of the New York Rheumatism Association held on April 23, 1949, the following Officers were elected for the ensuing year : *President*, Edward F. Hartung ; *Vice-President*, Cornelius H. Traeger ; *Secretary-Treasurer*, Robert M. Lintz.

BOOK REVIEW

Report of the Royal Free Hospital Unit of Rheumatology for 1948. London. (No price given.)

This annual report is an index of the increasing efficiency with which the problem of the rheumatic diseases is being attacked today. The formation of similar units throughout the country is a welcome sign of a quickening interest in this important group of locomotion diseases. The role which these units will play in the future will soon be recognized as of primary importance to the Social economy.

The Royal Free Hospital Unit makes a plea for the reference of patients to these special centres *in the early days of the disability*. It would seem that the average patient is referred for specialist attention only after nine months of failure to respond to "the usual remedies"! The tragedy is that frequently no real diagnosis has been established, and no effective therapeutic countermeasures have been instituted. As a result the patient's mental attitude to his disability has become warped and fixed. He manifests an antagonistic scepticism to all forms of therapy or else a hopeless resignation to his misfortune. In each case he is unco-operative and rather helpless and hopeless. Despite these difficulties, however, it is interesting to note that the *average* stay in Hospital for rheumatoid arthritis throughout all age groups *is less than three months* and that the Royal Free Hospital Unit has had great success with the "neurosis group".

It would seem desirable that some basic standards of assessment should be agreed upon between the different units studying the rheumatic problem. Obviously criteria of diagnosis, classification, and assessment of improvement must be laid down if figures from different units are to be comparable and their combined experience is to carry maximum weight.

It is obvious that these units have many functions to perform: (a) they must provide a first-rate diagnostic service (this is self evident); (b) they must provide a first-rate treatment service and be capable of treatment-assessment by adequate control experiments; (c) they must provide a first-rate re-employment service, for without this the whole of the rehabilitation process becomes a mockery; (d) they must provide a first-rate research service working in association with a University; (e) they must provide a first-rate teaching service both for the training of the medical profession and the training of patients in how to adjust themselves in every way to their environment and to maintain that adjustment.

A Unit with so many functions requires team-work for efficiency and it is encouraging to see how medical men of varied interests are turning their attention to this problem today.

The Royal Free Hospital Unit must be congratulated on its report for the year 1948. We shall await with interest the published reports on the different research items that are mentioned, and we hope that other rheumatism unit reports will be available for the year 1949.

MEDICAL RESEARCH COUNCIL

The Medical Research Council have appointed a Standing Committee on Rheumatism under the Chairmanship of Sir Edward Mellanby. The other members are: Professor H. P. Himsworth (Chairman Elect), Sir Charles Harington, Professors J. H. Gaddum, G. F. Marrian, R. G. Cameron, E. C. Dodds, Sir Robert Robinson, Sir H. W. Florey, Professor H. J. Seddon, Drs. J. Reid, D. H. Collins, W. S. C. Copeman, and R. K. Callow (Secretary).

AMERICAN COMMITTEE TO STUDY RHEUMATISM

The U.S. Surgeon-General has appointed Dr. Philip Hench, of the Mayo Clinic, chairman of a committee to study new methods promising to alleviate rheumatic diseases. The other members are Dr. Walter Bauer, of Boston General Hospital; Dr. Granville Bennett, of the University of Illinois School of Medicine; Dr. Jerome W. Conn, of the University of Michigan; Dr. W. Paul Holbrook, of Tucson, Arizona; Dr. Robert Loeb, of New York; Dr. Fred Moore, of the University of Southern California School of Medicine; Dr. Jane A. Russell, of Yale University School of Medicine; Dr. Emil L. Smith, of the University of Utah School of Medicine; and Dr. Alfred L. Wilds, Professor of Chemistry, University of Wisconsin.

OBITUARY

Ralph Pemberton, President of the International League against Rheumatism since 1938, died of a coronary occlusion on June 17 at his home in Paoli, Pennsylvania. He was 72.

Ralph Pemberton was born in Philadelphia, Pennsylvania, in 1877. He graduated from the University of Pennsylvania and the University of Pennsylvania Medical School with the degrees of B.S., M.S., and M.D. After working at the Philadelphia General Hospital he practised in Philadelphia. While at the hospital he was deeply distressed and interested in the plight of the many " rheumatics ", for whom morphia offered the only form of treatment and relief. His practice naturally centred around this interest, and he became known for his writings on the subject. When the World War 1914-18 came, he was assigned, as a Major in the Medical Corps of the United States Army, to the intensive study and treatment of arthritis. He carried on the observations begun in the Presbyterian Hospital in Philadelphia (where he served for eighteen years). The result of these studies stimulated increased nation-wide interest.

After the war he returned to research as Woodward Fellow in physiological chemistry at the Pepper Laboratory of the University of Pennsylvania. Before the war (1912), he had already taken a course of graduate study in Berlin and Strassburg. On his return from Europe he inspired a group of younger men to help him and so to build up a well-known clinic. In 1926 he was appointed chairman of the American Committee for the Study and Control of Rheumatic Diseases, the American Branch of the International League against Rheumatism, which had been organized in 1925. In 1933 this committee organized the American Rheumatism Association, of which Dr. Pemberton later became president. His wisdom and guidance were invaluable, as he had been a member of the council of the International League from its beginning. In 1938 he became President of the International League against Rheumatism. His illness tragically prevented him from enjoying the recent congress, held in New York, for which he had striven for eleven years.

Dr. Pemberton was awarded the Meritorious Service Medal of the Commonwealth of Pennsylvania in 1939. In 1944 he was made the first president of the Pan-American League for the Study and Control of Rheumatic Diseases. He was national consultant in Rheumatism and arthritis under the programme of wartime graduate medical meetings. In 1946, in recognition of his research on arthritis and for work on physical medicine, he was awarded the Gold Key of the American Congress of Physical Medicine.

At the Abbington Hospital Dr. Pemberton was physician in chief, Service of Rheumatoid Diseases; and he was made Professor of Medicine, Graduate School, University of Pennsylvania in 1931; both positions he held until his death. He was chairman of the committee on rheumatic disease of the Department of Health of Philadelphia; Honorary Fellow of the Royal Society of Medicine, London, England; Honorary Member of the Societatea Anatomo-Clinica, Bucharest, Rumania, of the Liga Argentina Contra el Reumatismo, of the Liga Uruguaya Contra el Reumatismo, and of the Liga Brasiliera Contra o Reumatismo; and an Honorary Member of the International League against Rheumatism.

Dr. Pemberton was known for his many excellent writings on arthritis, physical medicine, and rehabilitation of the disabled soldier. He was a pioneer in the scientific study of rheumatic disease, which he was convinced was a systemic condition that should be studied against the background of all available knowledge and with as profound an understanding as possible of basic metabolism. The whole subject was, Dr. Pemberton felt, " a big horse to ride " and one well worthy of a lifetime effort, both because of the confusion of tongues in regard to the treatment and nature of rheumatoid diseases, and also because of the deep sociological distress brought about through the economic loss to individual sufferers and to society as a whole. He was therefore untiring and direct in his determination to solve the problem, with his great affection for people as the driving force.

He was a true internationalist, and made a host of friends all over the world. Both those he had met in his frequent travels and those with whom he had corresponded respected and admired him, and loved him for his cordial friendly manner. He was untiring in his efforts to organize world co-operation —and this not only in the studies in which his interest lay; he never forgot that friendship and international goodwill work for world peace. This interest may even be said to have been closer to his heart than the study of rheumatic disease.

His death will be a misfortune to his friends, and his wise opinions and counsels will be missed by the world organizations with which he was associated. He was a great man in a difficult field of medicine.